Serum Lipoprotein (a) levels in Thromboangiitis Obliterans: A case control study

Serum Lipoprotein (a) levels in Thromboangiitis Obliterans:

A case control study

A Dissertation submitted in partial fulfillment of

M.S (General Surgery) branch I Examination of

The Tamil Nadu Dr. M.G.R. Medical University, Chennai,

To be held in 2014.

CERTIFICATE

This is to certify that the dissertation “Serum Lipoprotein (a) levels in Thromboangiitis Obliterans” is a bonafide work of Dr. Prerit Thomas Jacob, towards the MS Branch 1(General Surgery) Examination of the Tamil Nadu Dr. M.G.R Medical University, Chennai to be conducted in 2014.

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Dr. Prerit Thomas Jacob

Table of Contents

Acknowledgement	4
Introduction	8
Aim and objectives	11
Review of literature	12
Thromboangiitis Obliterans	12
Lipoprotein (a)	34
Lipoprotein (a), Peripheral Arterial Disease and Thromboangiitis Obliterans	42
Material and methods	47
Results and analysis	49
Summary of results	75
Discussion	76
Limitations of the study	81
Bibliography	82

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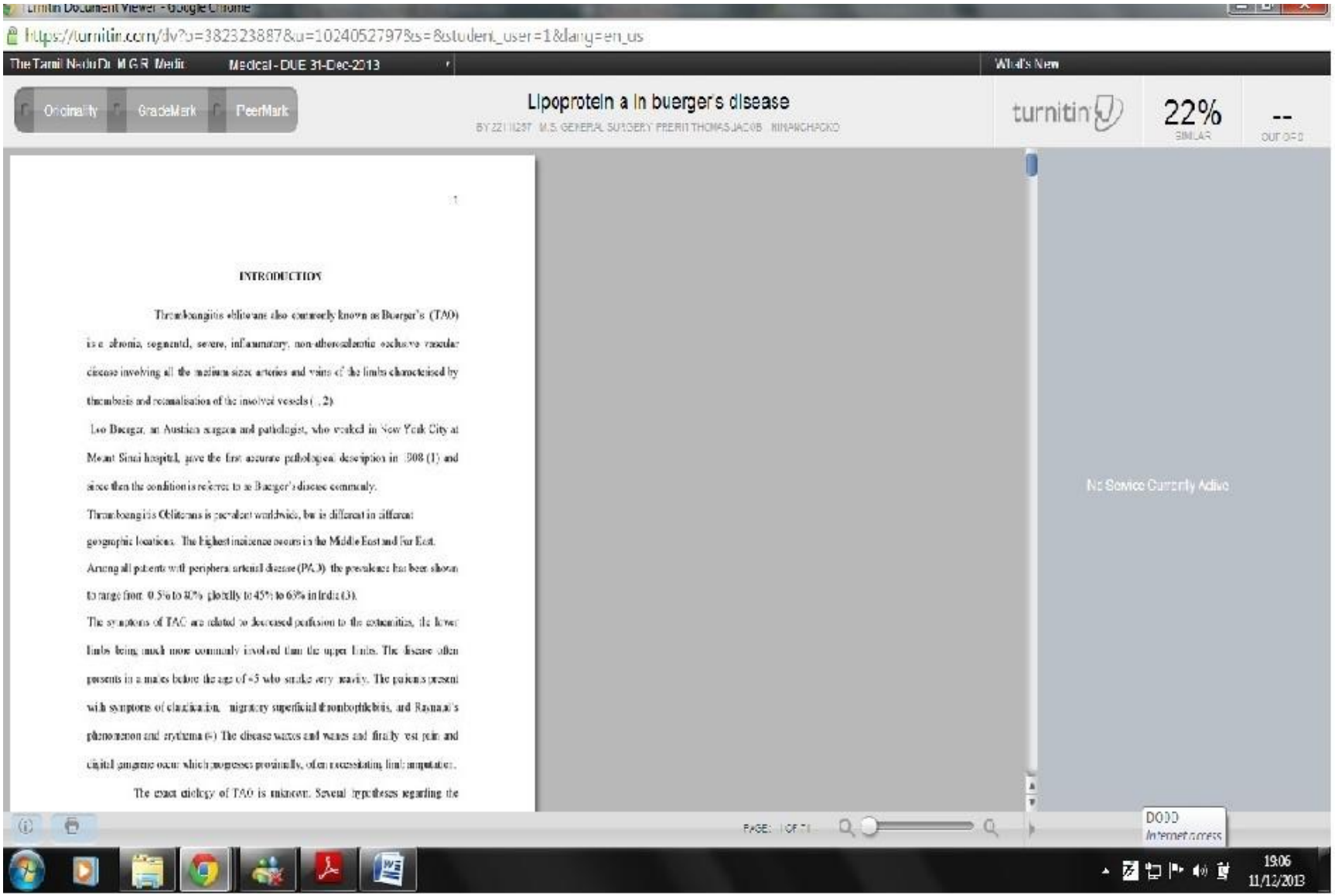
1 INTRODUCTION Thromboangiitis obliterans also commonly known as Buerger's (TAO) is a chronic, segmental, severe, inflammatory, non-atherosclerotic occlusive vascular disease involving all the medium-sized arteries and veins of the limbs characterised by thrombosis and recanalisation of the involved vessels (1, 2). Leo Buerger, an Austrian surgeon and pathologist, who worked in New York City at Mount Sinai hospital, gave the first accurate pathological description in 1908 (1) and since then the condition is referred to as Buerger's disease commonly. Thromboangiitis Obliterans is prevalent worldwide, but is different in different geographic locations. The highest incidence occurs in the...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Thromboangiitis Obliterans is prevalent worldwide, but is different in different geographic locations. The highest incidence occurs in the Middle East and far East. Among all patients with peripheral arterial disease (PAD) the prevalence has been shown to range from 0.5% to 80% globally to 45% to 63% in India (3).
The symptoms of TAO are related to decreased perfusion to the extremities, the lower limbs being much more commonly involved than the upper limbs. The disease often presents in a males below the age of 45 who smoke very heavily. The patients present with symptoms of claudication, migratory superficial thrombophlebitis, and Raynaud's phenomenon and erythema (4) The disease waxes and wanes and finally rest pain and digital gangrene occur which progresses proximally, often necessitating limb amputation.
The exact etiology of TAO is unknown. Several hypotheses regarding the
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INTRODUCTION

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The exact etiology of TAO is unknown. Several hypotheses regarding the pathogenesis are postulated but a tobacco associated vasculopathy is most accepted (2, 5),

possibly due to hypersensitivity to tobacco antigens (6) and also an underlying genetic predisposition (3).

Complete cessation of smoking is the most important step in the treatment of this debilitating disease. Often aspirin (salicylic acid) is prescribed to patients (3) and lumbar symphathectomy provides short term benefit. Approximately 43% of patients diagnosed with the condition but who continue to smoke are at risk to have a digit or extremity amputated (2).

Lipoprotein (a) or Lp (a) has been reported to have an association with atherosclerotic disease, especially coronary artery disease (7) stroke (8) and also peripheral arterial disease (PAD) (9). It is also observed to be elevated in cases of Buerger's disease (10). The physical structure of lipoprotein (a) is extremely similar to that of plasminogen competing with it for its binding site, and reducing fibrinolysis (11). It also has a role in thrombogenesis and atherosclerosis.

Lipoprotein (a) levels are predominantly determined genetically an. Environmental factors, including the classical vascular risk factors seem to have a weak association as causative factors. There is a definite variation among populations with Asians having comparatively higher serum concentrations of Lipoprotein (a) when compared to the Western population (12). However, there are very limited studies specifically investigating Lp (a) TAO among Asians or any other population. There are only few reports of TAO with elevated levels of lipoprotein (a) (10, 13).

Niacin has been proven to have an effective role in reducing serum Lp (a) levels in coronary artery disease in a Caucasian population (14). The available lipid modifying drugs currently in the market have a negligible effect on lipoprotein (a) levels with the

exception of niacin. In TAO, it might be worthwhile to study the prevalence of lipoprotein (a) in such patients as it has a role in thrombogenesis. It may be hypothesized that if patients with TAO are found to have elevated Lp (a) levels, further trials may be designed to test the therapeutic efficiency of niacin in this subgroup of PAD especially as this drug is cheap and safe. Hence this study on "Prevalence of elevated lipoprotein (a) in diagnosed cases of Thromboangiitis Obliterans presenting in a tertiary care centre in South India" was conducted.

Aims and Objectives

Aim

To study the association between lipoprotein (a) levels and thromboangiitis obliterans.

Objectives:

1. To compare the levels of lipoprotein (a) in TAO to age and sex matched controls.
2. To study the association between lipoprotein (a) levels and severity of disease in TAO.

Serum Lipoprotein (a) levels in Thromboangiitis Obliterans

REVIEW OF LITERATURE

Thromboangiitis obliterans, also commonly referred to as Buerger's disease is a non-atherosclerotic inflammatory condition that most commonly involves the small and medium sized arteries and veins of the upper and lower limbs. (1, 2)

History

Thromboangiitis Obliterans (TAO) was first reported by Felix von Winiwarter, an Austrian physician, a native of Vienna in 1879 in an article titled "A strange form of endarteritis and endophlebitis with gangrene of the feet". He described a 57-year old male patient who had an unusual occlusion of the vessels of the lower limbs. He attributed it to tissue growth from intima and the name "endarteritis obliterans" was proposed. Three years earlier, bacteriologist Carl Friedlander referred to it as arteritis obliterans. However Leo Buerger, an Austrian surgeon and pathologist, who worked in New York City at Mount Sinai hospital, gave the first accurate pathological description from amputated limbs of 11 Jewish migrant patients and presented his paper on TAO in 1908.(1) Based on the findings he deduced that acute inflammation of the vascular wall led to the formation of thrombus, which later, during its organization, resulted in intimal hyperplasia and hence called it "Thromboangiitis obliterans" to distinguish it from "arteriosclerosis obliterans".(1) Later this disease was referred to as "Winiwarter–Buerger" syndrome, "Buerger's disease" or "Thromboangiitis Obliterans".

Buerger's disease is one of the two main types of premature peripheral arterial disease (PAD) in patients who are not diabetic. Peripheral arterial disease includes either peripheral arterial occlusive disease which is atherosclerotic in nature or TAO which is non-atherosclerotic in nature.

Epidemiology

Thromboangiitis Obliterans is prevalent all across the globe. But the maximum incidence occurs in the Middle East and Far East (3). At the Mayo clinic in Rochester, USA, the percentage of diagnosed cases of Buerger's disease reduced significantly from 104.3 per 100,000 patients in 1947 to almost 12.6 per 100,000 patients in 1986. (15) The prevalence of the condition in the general population in the country of Japan was estimated at 5/100,000 persons in the year 1985 (3) and it has also shown a decreasing trend (16). The prevalence of the TAO among all the patients with peripheral arterial occlusive disease was found to be as low as 0.5 to 5.6% in Western Europe to as high as 45 to 63% in India and 16 to 66% in Korea and Japan. In a particular subset of people, the Ashkenazi Jews, it is seen in up to 80 percent of the patients with peripheral arterial disease (3). It is also seen with increased frequency in Eastern Anatolia, Turkey. (17) In India, in a report from Bangalore, the proportion of patients with TAO among those admitted with peripheral vascular disease decreased from 63.9% in 2001 to 37.2% in 2005. (18)

Buerger's disease is a condition which mainly affects young males who smoker heavily. Earlier, they represented over 90% of affected patients, but later, in the 1980s

women have constituted an increasing percentage of the diagnosed cases. (> 20% in some studies) (5).

Etiology & Pathogenesis

Smoking

The etiology of Buerger's disease remains evasive, but the disease is known to have a strong link with tobacco consumption and smoking (5). The typical patient is a male who is young and smokes heavily and the use of or exposure to tobacco is of prime importance to the triggering or initiation and progression of this debilitating disease (3). Urinary levels of cotinine which is a major metabolite of nicotine, used as a measure of active smoking revealed a very close relation with Buerger's disease (19). Both the decrease in prevalence of Buerger's in the US among all patients and the increasing prevalence among females are attributed to a corresponding change in tobacco use. (5, 15).

There is a high prevalence noted in Southeast Asia among populations of low socioeconomic class who smoked bidis (a homemade surrogate for cigarettes, without filters from low quality tobacco.) These bidis contain more nicotine and toxic substances as compared to cigarettes. (18, 20). Rahman et al compared those who smoked more than 20 bidis per day to those who smoked less than 10 bidis per day and concluded that the odds ratio for developing TAO was significantly higher (58.28) in the former as

compared to the latter. (20). Although a few researchers agree that Buerger's disease can occur in non-smokers (21), most view exposure to smoke or a history of smoking present or past as essential for the diagnosis.(22) Harkavy was the first researcher to suggest the possibility of a hypersensitivity reaction to antigens present in tobacco in Buerger's disease patients (6).

Cannabis consumption has also been noted more frequently in patients with TAO compared to controls. This may be because cannabis consumption is usually associated with smoking (23).

Immune- mediated

Altered autoimmune responses could play a part in Buerger's disease. Autoimmune phenomenon has been suggested because of the presence of high titers of anti-endothelial cell antibodies in patients with this disorder (24). Adar et al demonstrated that patients with the disease have an elevated cellular sensitivity to type I and II collagen (which is found in vascular smooth muscle) and elevated circulating antibodies to Type I and II collagen as opposed to patients with arteriosclerosis obliterans or healthy males (25). An immune mediated endarteritis has also been suggested as immunochemical studies have demonstrated deposition of immunoglobulins and complement factors along the vascular elastic lamina in a linear fashion due to an antigen in the intimal layer. T-cell mediated cellular immunity and B-cell mediated humoral immunity which along with the activation of macrophages or dendritic cells in the intima induces endarteritis within the vessel (26).

Endothelial dysfunction

Impaired peripheral endothelium-dependent vasodilatation has been documented in patients with Buerger's disease, while non endothelial mechanisms of vasodilatation seem to be unaffected (27).

Genetic predisposition

De Moerloose et al discovered a significantly low frequency of the HLA-B12 antigen among people with Buerger's disease (2.2% *vs*. 28% in controls) implying a resistance gene (28). Some researchers have noted an increased frequency of HLA-A9 and HLA-Bw5 or HLA-B8, B-35 and B40 antigens in patients form Eastern European and Asian countries (4). Importantly the prevalence of Buerger's disease is higher in Eastern Europe and Asia than in the US. Similar to many other autoimmune diseases, TAO may possibly have a certain genetic predisposition without a direct "causative" gene mutation.

Hypercoagulability

A close association between thrombophilic diseases like antiphospholipid syndrome and hyperhomocysteinemia and Buerger's disease is noted (29). TAO is also linked with a higher prevalence of anticardiolipin antibody (aCL). The presence of an n increased antibody titre among these patients is linked to increased morbidity especially major limb amputations (30).

Oral infection – inflammatory pathway.

Researchers have raised the possibility of an etiologic link between Buerger's disease and long standing infections such as oral bacterial infections. Smoking, periodontitis and Buerger's disease in certain studies have been shown to be linked. Smoking worsens periodontitis and it is postulated that it aggravates the oral infection. Using PCR, the bacteria found in the plaque was similar to that in the mouth with *Treponema denticola*, being present in most of the arterial specimens studied. and less commonly Campylobacter rectus and Porphyromonas gingivalis (31).

Clinical Presentation

The disease has often presented with symptoms of distal ischemia in a young male who is a heavy smoker with most common involvement of extremity arteries and less often non-extremity arteries and nerves.

Extremity arterial involvement

This initiates with involvement of the smaller distal vessels of the lower limb and hands as a manifestation of infra-popliteal or infra-brachial occlusive disease, the lower limbs being much more commonly involved than the upper limbs. Presenting symptom may be claudication, affecting the feet, legs, hands and arms, typically arch or forefoot and later calf. The pain which starts in the extremities could radiate to more central parts of the body (3). Trophic nail changes and ischemic ulcerations develop at an early stage in the natural history of the disease. These are mostly found in the toes and fingers of the patient. Critical limb ischemia (CLI) is manifested as ulcerations and digital gangrene with chronic ischemic rest pain. Upper extremities are involved in up to 90% of cases unlike in atherosclerosis. Symptoms in upper limbs are similar to those of lower limbs in addition to Raynaud's phenomenon (usually asymmetrical). 43% of patients may demonstrate involvement of all the 4 limbs. (4)

Non-extremity arterial involvement

Non extremity arteries are not so commonly affected. Even and the coronary, mesenteric (32) and cerebral arteries (33) has been described to be involved. Cases of aortic and even multiorgan arterial involvement have been described (34).

Gastrointestinal manifestations of the disease due to involvement of certain arteries supplying the gut have been rare and isolated.; however, intestinal symptoms and signs due to stricture or perforation of the colon may become apparent long before symptoms of severe peripheral arterial disease in patients with TAO (3). If the smaller arteries are not involved it is highly unlikely for the larger arteries to be affected by the disease process. Involvement of internal thoracic arteries and the coronary arteries without the involvement of extremity vessels has also been reported (35).

Venous involvement

Superficial thrombophlebitis is observed in 38% of patients with TAO (5). This is a migratory thrombophlebitis or phlebitis saltans (without the presence of varicose veins) occurs as an early sign and can occur in 16 to 65% of patients who suffer from the disease. It predominantly affects small or medium sized veins in the feet, calves and forearms, and much less commonly the lesser or greater saphenous veins. The femoral or axillary vein involvement is a rarity. The lesions classically linear, but oft times may appear tuberous (4). Superficial thrombophlebitis is a clinical finding which differentiates Thromboangiitis obliterans from various vasculitides and atherosclerosis, though it may also be seen in Behçet's Disease. Superficial thrombophlebitis may predate the onset of ischemic symptoms due to the occlusive nature of the disease and often parallels disease activity (36).

Nerve involvement

A thorough neurological examination may elicit a sensory deficit in up to 70% of patients (36).

Physical examination

A patient suspected to have Thromboangiitis obliterans should have a detailed physical and vascular examination. The peripheral pulses should be palpated. The radial, ulnar, dorsalis pedis or posterior tibial pulses may not be palpable. Auscultation, looking for arterial bruits, and measurement of the Ankle Brachial Pressure Index (ABI) should be performed. A negative Allen's test is highly suggestive of small vessel involvement in both the arms and the legs. Although nonspecific, it assesses the circulation and uncovers arterial compromise of the upper extremity (37). In the early stage, involved vessels are indurated and tender, and bruits are usually not detected. Careful examination should be performed for dependent rubor, cyanosis, cold extremities, ulceration and gangrene. The extremities should be examined carefully for superficial venous nodules and cords.

Natural history

The disease process in TAO begins in the small foot and hand vessels and then progresses proximally. The progression may be in continuity or a new lesion may occur in a different segment of the arterial tree (skip lesions). In the majority of patients, the lesions do not extend proximal to the popliteal artery in the legs or the brachial artery in

the hands. The collateral circulation is found to usually be poor, and ischemic ulcerations of the toes and fingers develop at an early stage of the disease.

The disease waxes and wanes, with intermittent periods of active disease and acute exacerbation of symptoms which alternate with episodes of remission. The number of attacks may vary from one to twenty with the mean being 5.4 (38). The duration of remission may last up to years and may permanently subside if the patient stops smoking. Exacerbations are usually related to exposure to cigarette smoke. The virulence of the disease is maximum in the 3rd to 5th decade but may be lesser in older people as opposed to the temporal pattern than is seen in atherosclerosis. Shionoya didn't report new ulcer formation in TAO affected individuals older than 60 years (4). Patients with Buerger's disease very often are affected by severe ischemic pain and tissue loss which ultimately lead to minor and major limb amputation. In a study done by Cooper et al during a 15.6 years of follow up of 111 patients the risk of any extremity amputation was 25%, 38% and 46% at 5, 10, and 20 years respectively. The risk of major amputation amounted to 11%, 21% and 23% respectively (39). But after cessation of smoking according to Olin et al only 2 out of 43 (5%) patients underwent amputation (5). Life expectancy is also reduced in patients with TAO (52.8 years) compared to that of matched US population (39).

Diagnosis

Since there is no single confirmatory test to establish the diagnosis of TAO, a number of clinical signs and symptoms have been relied upon.

Diagnostic criteria of Shionoya - 1998 (22)

• A history of smoking

• Onset of symptoms before the age of 50 years;

• Infrapopliteal arterial occlusions;

• Either arm involvement or presence of phlebitis migrans;

• Absence of atherosclerotic risk factors other than smoking.

Diagnostic criteria of Olin - 2000 (2)

• Age under 45 years;

• History of recent/current tobacco use

• The presence of distal-extremity ischemia indicated by claudication, pain at rest, ischemic ulcers or gangrenes and documented by non-invasive vascular testing;

• Exclusion of autoimmune diseases, hypercoagulable states and diabetes mellitus;

• Exclusion of a proximal source of emboli by echocardiography or arteriography;

• Consistent arteriographic findings in the clinically involved and non-involved limbs.

Doppler ABI is a precise and affective method to document the presence and severity of lower extremity peripheral arterial occlusive disease. The most accurate studies are those which use objective methods of diagnosis, the Doppler being one of them. An "ankle-brachial index" (ABI) is calculated by dividing the ankle systolic pressure measured with a blood pressure at the level of the malleolus by the higher of the two measured brachial pressures. An ABI which is greater than 1·0 is considered normal. It decreases to 0·50–0·90 in patients presenting with claudication and to even lower levels in those patients who have pain at rest or tissue-loss (ulcers) (40).

Differential diagnosis

The following differential diagnoses are to be considered for TAO.

- Atherosclerotic PAD
- Systemic vasculitis
- Scleroderma
- Emboli
- Hypercoagulable states
- CREST syndrome
- Repetitive trauma
- Drugs (ergot)

Atherosclerosis is clinically distinguished from TAO by the very distal nature of involvement of vessels of the legs and arms in the latter. A negative Allen's test in a young male smoker who presents with lower limb ulcerations is strongly suggestive of TAO (37). However, an abnormal result can also occur in certain other types of small vessel occlusive diseases of the upper limbs such as CREST syndrome, scleroderma, repetitive trauma, vasculitis, emboli and hypercoagulable states.

The following features distinguish Buerger's disease from atherosclerosis which has a similar clinical presentation.

Clinical Differences between Atherosclerosis and Buerger's Disease (4)

Patient Characterestics	**Atherosclerosis**	**Buerger's disease**
Age at presentation	>40	20-40
History of tobacco use	+	++
Other risk factors	+	+/-
Upper extremity involvement	-/+	+
Proximal vessel involvement	++	-/+
Migratory superficial thrombophlebitis	-	+

++ = invariably present; + = usually present;

+/- = occasionally present; -/+ = uncommonly present

\- = not a feature of the disease

Laboratory tests

No specific test to diagnose Buerger's disease is available. Laboratory tests are done to exclude alternative diagnoses. As opposed to other types of vasculitis, in patients with TAO, the acute phase reactions like Erythrocyte Sedimentation Rate or C - reactive protein level are usually within normal range (36). Occasionally an increased ESR, fibrinogen level and platelet count can be found in patients with tissue loss.

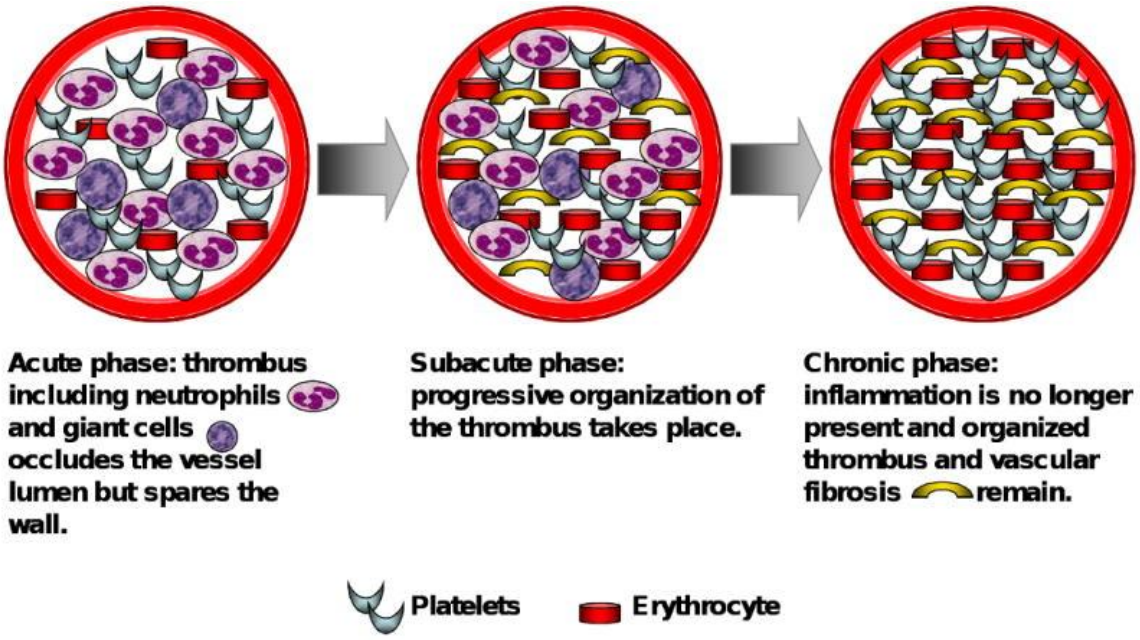
Other causes of vasculitis can be excluded by performing complete blood count, serum creatinine concentrations, rheumatoid factor, antinuclear antibody level, VDRL

antigen, liver function tests, serum complement levels (C_1 – C_4), serologic markers specific for CREST (calcinosis cutis, Raynaud's phenomenon, sclerodactyly and telangiectasia) syndrome and scleroderma.

Hypercoagulopathies may be ruled out by performing Antithrombin III Level, Antiphospholipid antibodies, Factor V Leiden levels, Protein C level, Protein S level, and Prothrombin time and partial thromboplastin time. Anticollagen antibodies, Antiphospholipid and antielastin are occasionally found, although titres may be low (4).

Pathology

Histopathological specimens are obtained usually from amputated limb tissue or biopsy specimens from superficial inflamed veins. Findings are almost the same in the involved veins and arteries. Although no confirmatory histopathological features are established, the characteristics are unique for this disease to distinguish it as an entity very much distinct from conditions like atherosclerosis, necrotizing vasculitides or idiopathic arterial thrombosis.The findings are very likely to vary, depending upon the duration of the disease. They have a high chance to be diagnostic if in the acute phase, a biopsy of a segment of a vein with superficial thrombophlebitis is done (2).



Pathophysiological phases of Thromboangiitis obliterans (36)

The striking characteristic of Buerger's disease is the occlusive, highly inflammatory (cellular) thrombus with presence of microabscesses and multinucleated giant cells visualized within the thrombus during what is known as the acute phase (36). This thrombus is very different from the bland thrombus seen in hypercoagulable conditions. The vessel wall may show features of ongoing inflammation although to a much lesser extent. Segments of diseased arteries and veins are found to be present between segments of unaffected vessels in TAO as opposed to atherosclerosis where there is more diffuse arterial involvement (4). Rarely few segments of blood vessels may also have a thrombus not infiltrated with the typical inflammatory cells seen in Buerger's disease. The structure of the vessel wall is usually not altered, including the internal elastic lamina and media, a characteristic which firmly distinguishes TAO from

arteriosclerosis and from many other types of systemic vasculitis. There is no smooth muscle necrosis within the vessel wall or any evidence of fragmentation of the elastic lamellae: which is very often seen in necrotizing vasculitides.

If the disease has progressed to an intermediate phase (subacute) then organization of the thrombus which is progressive in nature within the arteries and the veins is seen. Finally in the end stage (chronic), an organized thrombus with fibrosis is seen within the vessels (3, 41). In advanced stages of the condition, the lesions progressively become less distinctive. At this time an organized and re-canalized thrombus may exist. They thus provide a focal residual inflammatory reaction which may just be sufficient to suggest possible TAO (2).

Other findings of note are onion shaped recanalizing of vessels in the involved arteries, adventitial fibrosis in the absence of medial fibrosis, endothelial swelling of the vasa vasorum and edema beneath the external elastic lamina (41). These findings would probably be helpful in coming to a differential diagnosis in patients with unusual clinical presentations.

Ultrasonography

Non-invasive vascular studies are used to quantify and confirm the location and degree of peripheral arterial occlusive disease. Aortic ultrasonography and echocardiography are helpful in ruling out a proximal embolic source. Duplex Ultrasonogram is another very useful tool.

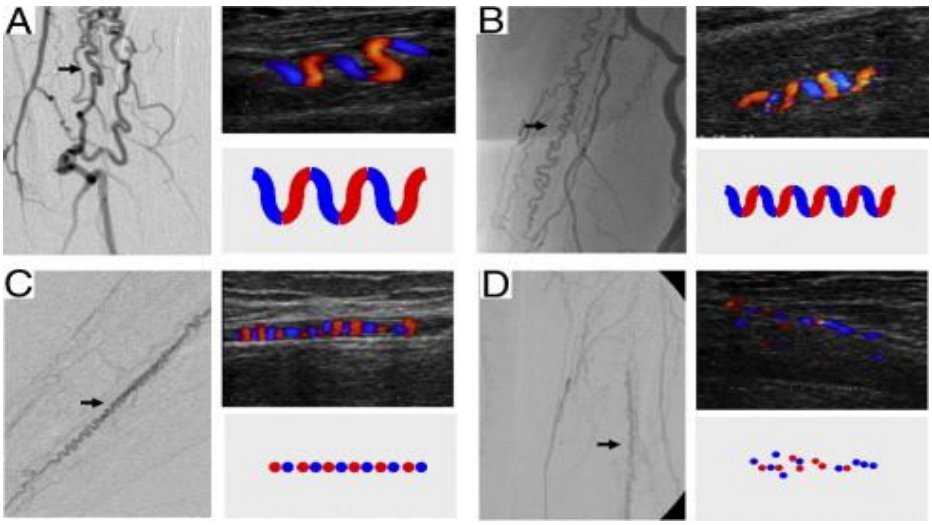
Corkscrew collaterals are classified into 4 types by artery amplitude and color Doppler flow formation pattern.

Type I, large snake sign with an artery amplitude >5 mm being similar to or greater than amplitudes of original conduit arteries.

Type II, small snake sign with an artery amplitude >3 and ≤5 mm, most of the corkscrew collaterals with an amplitude of ≤3 mm being shown as dot signs

Type III, dot sign with corkscrew collaterals with an amplitude >1 and ≤3 mm shown as a striped pattern of the side row.

Type IV, small dot sign with most of the corkscrew collaterals with an amplitude of ≤1 mm shown as random points but not a striped pattern (42).



A: large snake sign **B**: small snake sign
C: dot sign with corkscrew collaterals **D:** small dot sign

Arteriography is considered in patients in whom clinical features and ancillary laboratory studies fail to confidently establish the diagnosis. The findings that most characterize TAO are the following: smooth arterial walls of unaffected arteries, multiple peripheral segmental occlusions which are known as "skip lesions". Presence of direct corkscrew collateral vessels that follow the course of the involved/diseased vessel (Martorell's sign) may be visualized. The collaterals represent the markedly enlarged vasa vasorum of the diseased vessel (43).

Characteristic angiographic Findings in Buerger's Disease (4, 43)

- Multiple segmental arterial involvement (skip lesions) 100%
- Smooth vessel wall in unaffected arteries 100%
- Abrupt arterial occlusions 42-100%
- Smoothly tapered arterial occlusions 40-41%
- Tortuous or corkscrew type collaterals 100%
- Direct collaterals (Martorell's sign) 80%
- "Tree root" or "spider leg" collaterals 40%

The diagnostic value of many imaging methods such as computerized tomography (CT scan) and magnetic resonance imaging (MRI) in TAO still remains unclear. A proximal source of arterial embolism or a need to define the anatomy and extent of the diseases vessels may warrant an invasive contrast angiography or a CT or MRI.

Management and Treatment

The most important step in the treatment for TAO is **smoking cessation**. Even the use of one or two cigarettes per day or abuse of smokeless tobacco (chewing tobacco or using nicotine containing patches) has the potential to keep up the disease activity (44). Affected individuals who continue to smoke have been shown to be at risk for amputation of fingers and toes (3). About 40% of these patients who are unable to quit smoking

require having a digit or extremity amputated, as compared to five percent of patients who abstain from smoking (5).

Supportive care is directed towards achieving the maximum blood supply to the diseased limbs as possible. Special caution is taken to avoid thermal, chemical or mechanical insult especially from poorly fitting footwear.

Despite the important role of an inflammatory process in the pathogenesis of Buerger's disease, anti-inflammatory agents e.g. steroids offer no benefit. Although aspirin (acetyl salicylic acid) is often prescribed to patients, the real benefit of this or other oral anti-clotting drugs has not been demonstrated (3). Intravenous therapy with Iloprost (a prostaglandin analogue) is shown to be superior to aspirin in achieving pain relief. This drug has also been proven to be better in the healing of all trophic ulcers and reduces the risk of amputation (45). Medications such as clofibrate, (46) cyclophosphamide, (47) and calcium channel blockers have been used with varying success. Other vasodilators, namely alpha-blockers or sildenafil, may be of some benefit, having not been evaluated sufficiently prospective clinical trials (36). Induced hypervolemia and prostacyclins are effective in the treatment of critical limb ischemia in TAO.

In patients who are poor candidates for revascularization procedures due to the distal nature of their disease, augmentation of perfusion to the diseased limbs is achieved by the use of intermittent pneumatic compression of the foot and calves (48). The use of streptokinase given intra-arterially as thrombolytic therapy has been evaluated in patients with gangrene or pre-gangrenous lesions and has shown to be of some benefit (3).

Surgical modalities include, arterial reconstruction, bypass vein grafts, lumbar symphathectomy, and when required, amputation. Sympathectomy gives temporary pain relief and ulcer healing but no confirmed long term benefit. A laparoscopic method of sympathectomy has also been used (49). In patients with Thromboangiitis obliterans, surgical revascularization usually is not a feasible option because of the distal and diffuse nature of the condition. Bypass surgery may probably be considered in very select patients with CLI and suitable distal target vessels (36). Neovascularization is one of the principles of treatment of chronic ischemia. Both periosteal elevation and distraction osteogenesis have been shown to increase neovascularistion (50).

Newer modalities like microvascular omental transfer (51) and extended endovascular recanalisation (52) have been tried. Angiogenesis by autologous bone marrow mononuclear cell implantation (53) and gene therapy have shown promise. Experimentally, spinal cord stimulator and (VEGF) vascular endothelial growth factor have been used in patients with TAO (36). However, the ideal modality for treatment of TAO is still undecided.

Lipoprotein (a)

Elevated Lipoprotein (a) or Lp (a) level has been reported to have a pathogenetic role, in atherosclerotic vascular disease and Thromboangiitis Obliterans. It was discovered half a century ago in 1963 by a Norwegian physician investigator Kare Berg (54). In 1987, the human gene which encoded this protein was cloned. Lipoprotein (a) is considered to be a vital molecule because its levels are genetically determined and have a very weak association with environmental factors, including the classically described vascular risk factors.

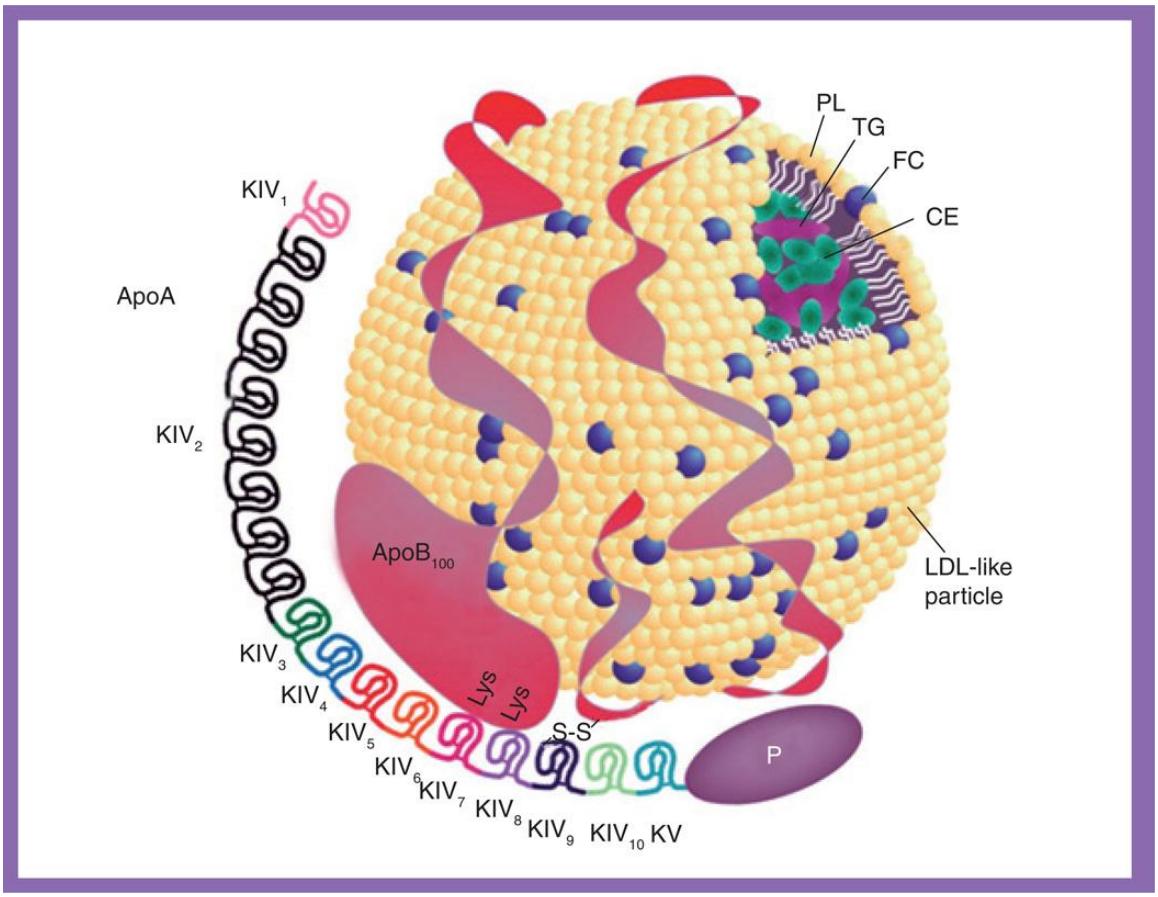
Structure

It is a lipoprotein subclass which is made of an ordinary cholesterol rich LDL particle which is combined with an additional protein. Similar to LDL, the lipoprotein (a) particle contains Apolipoprotein B100 (512,000 D), but has an unusual structure in that it additionally consists of Apolipoprotein a (apo[a]) (275,000-800,000 D), which is covalently linked by a disulfide bond to apolipoprotein B100 (55).

Lp (a) exhibits remarkable size heterogeneity (56). Apo(a) is a large protein containing a series of amino acid repeats known as "kringles" containing 3 intrastrand disulfide bonds which are highly homologous to similar repeats found in the molecule plasminogen (11), (75–85% identical to the fourth kringle of plasminogen). There are a total of 11 apo(a) kringle sequences; ten of these are present as single copies, but the remaining 1(K4 type 2) varies in copy number which is genetically determined and thus results in extremely high degree of inter-individual polymorphism in the molecular mass of apo(a). The kringle IV repeats may vary from 10 to >50, each of these variable kringle IV consisting of 114 amino acids (57). These variable apo (a) sizes are known as "apo

(a) isoforms". The larger isoforms are compromised with respect to protein folding, transport, and secretion. Thus, the number of apo (a) KIV2 repeats is found to be inversely proportional to plasma lipoprotein (a) levels.

Structure of Lipoprotein (a)



Genetics of Apoprotein (a)

Lipoprotein (a) plasma concentrations are mainly controlled by the apolipoprotein (a) gene and highly heritable. [LPA is a large gene found on chromosome 6q26-27 (adjacent to the plasminogen gene). The inter-individual variation in Lp (a) levels is 90% genetically determined by the *LPA* locus which determines heritability of plasma levels of the molecule (58).

Apo (a) proteins differ in mass predominantly due to size polymorphism [KIV-2 VNTR], which is caused by the kringle IV repeats within the LPA gene. The genetically determined KIV2 repeat size has an effect on the final size of the apo(a) protein i.e. this size variation at the gene level is invariably expressed on the protein level also (11, 57).

Synthesis and catabolism of Lp (a)

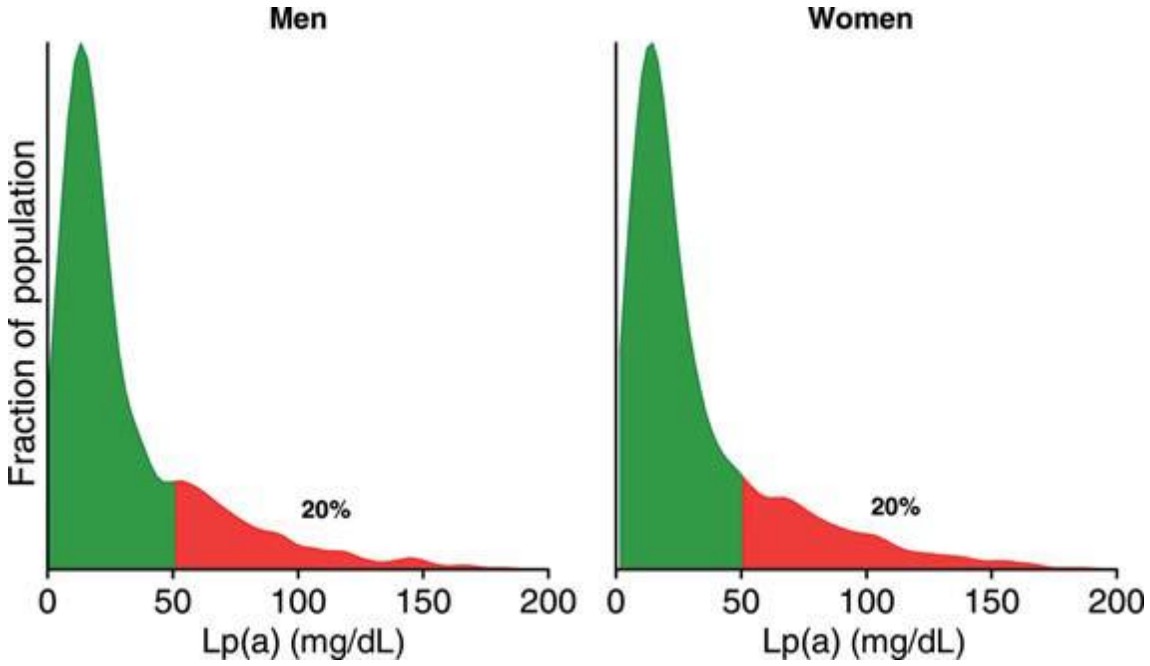
The liver cells (hepatocytes) express Apo (a) and the assembly of apo (a) and LDL particles probably take place at the outer hepatocyte surface. The half-life of lipoprotein (a) in the circulation is about three to four days (59). Until the precursor protein is released from the cell, Lipoprotein (a) is not fully synthesized; hence the rate of production of the larger isoforms is a limiting factor for the plasma concentration.

The sites and mechanisms of Lp (a) catabolism are not well understood. A minor pathway of Lp (a) metabolism is uptake via the LDL receptor. The kidney has been found to play a role in Lipoprotein (a) clearance from plasma.

Plasma levels of Lp (a)

In the general population plasma levels of Lipoprotein (a) have been found to range over 1,000-fold between individuals. And yet the plasma Lipoprotein (a) in a particular individual remains constant throughout his/her life from < 0.2 to > 200 mg/dL. This characteristic range of concentrations has been noted in all populations studied so far. In the study by Ashavaid et al from India, in normal subjects of both sexes, the

median level of Lipoprotein (a) was 12.9 mg/dl (60). Mohan et al reported a geometric mean of 19.4 mg/dl in healthy adults from South India (61).



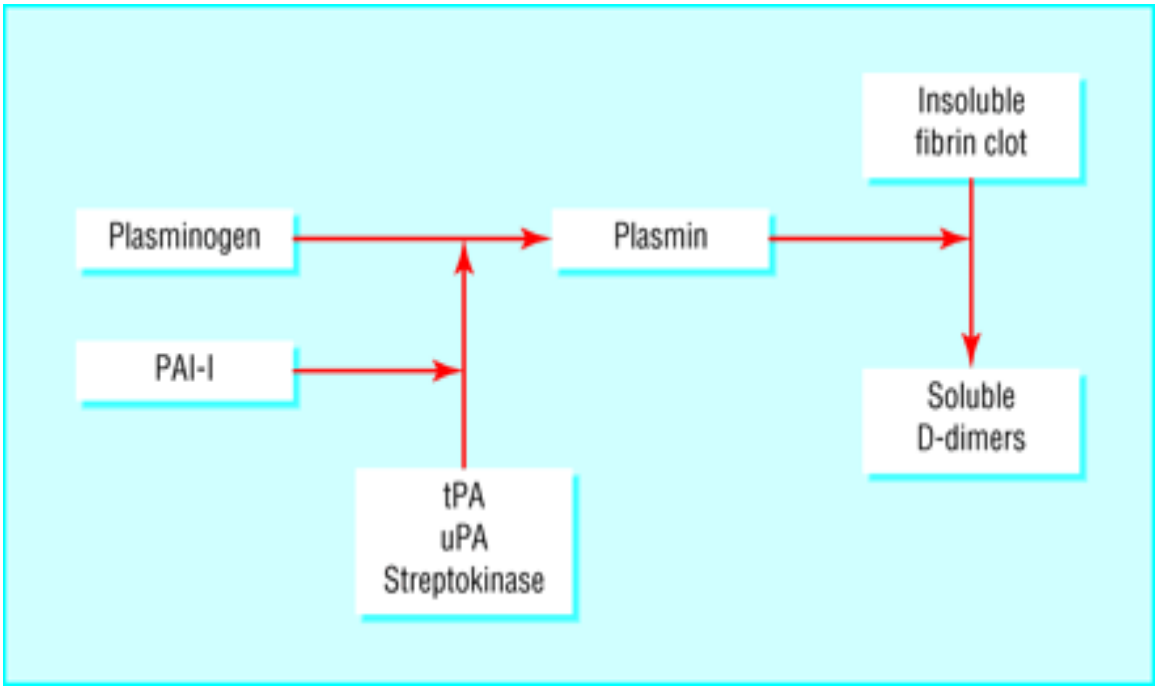
Typical distributions of lipoprotein (a) levels in the general population : These graphs are based on non-fasting fresh serum samples from _3000 men and 3000 women from the Copenhagen General Population Study collected from 2003 through 2004.2 Green color indicates levels below the 80th percentile, whereas red color indicates levels above the 80th percentile.

When the mean concentrations between multiple world populations were studied, it was found interestingly that populations of African descent compared to Asian, Oceanic, or European populations had a 2-3 fold higher Lipoprotein (a) plasma concentration. (62). A large meta-analysis of 36 studies showed the median value of lipoprotein to be 12.6 mg/dL. The blacks had a value more than 100% higher than that of whites (63). In all populations a general inverse correlation between apo (a) isoform size and Lipoprotein (a) plasma concentration has been observed; however, mean Lipoprotein (a) associated

with certain apo (a) isoforms varies between different populations. Sakurabayashi from Japan reported elevated Lp (a) levels to be one >30mg/dl (64). The Asians have higher serum concentrations of Lp (a) when compared to the general population in the United States (65) and the United Kingdom. This increase, found in indigenous Indians, is not affected by migration. Levels were almost twice as high in Indians as compared to Caucasians (12).

Function & Pathophysiological role of Lp (a)

The physiological or biochemical function of Lipoprotein (a)/apo (a) is not understood properly. People without Lp (a) or with very low levels of Lp (a) levels appear to be healthy. This indicates that plasma Lp (a) is certainly not vital to the cellular function under normal environmental conditions. Lp (a) could have a role with plasminogen activation or platelet function, or it could take part in the process of inflammation (66) or endothelial dysfunction (67).



PAI –Platelet Activation Inhibitor 1 tPA – tissue Plasminogen Activator uPA – Urine Plasminogen Activator

Lipoprotein (a) has a role in thrombogenesis and atherogenesis. The pathophysiological effects of Lipoprotein (a) which includes those on fibrinolysis are probably due to apo (a) since it has a high degree of homology (similarity) to plasminogen, (11) a critical factor in the fibrinolysis system. Plasminogen, is the zymogen of the primary thrombolytic enzyme, plasmin. Plasminogen receptors are widely distributed on blood cells and are present at extremely high density on endothelial cells. These receptors promote thrombolysis by accelerating plasminogen activation and protecting plasmin from inhibition. .By molecular mimicry, Lp (*a*) competes with plasminogen for receptors on cells, thrombolysis is inhibited and thrombosis promoted (68).

Lipoprotein's structure being similar to tissue plasminogen activator (tPA), it acts as a competitive inhibitor of tPA, thereby modulating the fibrinolytic system consistent with an atherogenic role (69). In addition, since Lp (a) stimulates secretion of Plasminogen Activation Inhibitor-1 (PAI-1) it culminates in thrombogenesis. Besides, because it contains LDL cholesterol, Lp (a) definitely contributes to atherosclerosis (70)

Importantly Lp (a) has a role in transporting the more atherogenic pro-inflammatory oxidized phospholipids which attract inflammatory cells to vessel walls (71) and leads to proliferation of smooth muscle cells. Endothelial cells play a key role in the initiation and propagation of the inflammatory response. One of the initial events in

atherogenesis is more binding of monocytes to endothelial cells and their entry into vessel walls. Lp (a) enhances the expression of intercellular adhesion molecule (ICAM-1) which supports the adhesion of various leukocytes including monocytes to the endothelial cell. It is suspected that these monocytes have an important contribution to plaque formation (72). Apoprotein (a) has been found to have potential for atherogenicity and plaque formation. It also has a key role in thromboembolic events resulting from plaque rupture.

Other functions that have been described are related to recruitment of inflammatory cells which occurs by interaction with beta-2 integrin Mac-1 (73), angiogenesis, and wound healing. Another theory suggested by Linus Pauling, is that Lipoprotein (a) is an adaptation of primates to L-gulonolactone oxidase (GULO) deficiency which has been found only in certain mammals. GULO is necessary to convert glucose to ascorbic acid (vitamin C), which is in turn needed to repair arteries; following the loss of GULO, those primates which adopted diets that were less abundant in vitamin C may have used Lp(a) as an ascorbic-acid surrogate to repair their arterial walls (74).

Lipoprotein (a) and cardiovascular disease

Lipoprotein (a) is considered as an important risk factor for cardiovascular diseases (75). Its high concentration has been proven to be one of the major risk factors for premature development of diseases like atherosclerosis and cardiovascular disease (7, 76). A similar risk associated with high Lp (a) levels has been reported by Beena et al from India (77). The Copenhagen City Heart Study revealed a stepwise increase in risk of myocardial infarction with corresponding increase in levels of lipoprotein (a), with no

evidence of there being a threshold effect. Extreme lipoprotein (a) levels predict a three to four fold increase in risk of myocardial infarction occurring in the general population (78). The largest epidemiological study till date on Lipoprotein (a) assessed the individual records of 126 634 participants in 36 prospective studies. Lipoprotein (a) concentration was weakly correlated with the presence of several known vascular risk factors: strongly with total and non-HDL cholesterol, apolipoprotein B100. It was correlated inversely with $\log_e$ triglycerides. Lipoprotein (a) levels were found to be twelve percent (95% CI: 8–16%) higher in women and eleven percent (4–17%) lower in people with diabetes (79). It is also found to be an independent risk factor for CAD in Non-Insulin Dependent Diabetic patients in a study from South India (61). In a study by Bhavani et al from Hyderabad higher levels of Lp (a) was observed in patients with essential hypertension compared to controls (80). High levels of Lp (a) has also been found in patients with stroke (8).

Lipoprotein (a), Peripheral Arterial Disease and Thromboangiitis Obliterans

Majority of the research work investigating Lp (a) and peripheral arterial occlusive disease has been predominantly done upon Caucasian populations (75). However, there are limited studies which specifically investigate Lp (a) and peripheral arterial occlusive disease in Asians or TAO in any population. In a report from Austria, patients with PAD had a significantly higher median level of Lp (a) compared to controls (76 v/s 47 mg/L) (81). In a study from Cambridge, UK, Lp (a) levels were measured in apparently healthy participants in the European Prospective Investigation of Cancer (EPIC)-Norfolk cohort, and the levels were associated with risk of PAD and CAD outcomes (82). The study by Hakim et al from Malaysia reported a significantly higher mean level of Lp(a) among PAD patients compared to controls (0.56 v/s 0.29 g/L) (83)

Lipoprotein (a) levels have been found to correlate with Ankle Brachial Pressure Index (ABPI) and more severe forms of PAD. In a study among Chinese Type 2 diabetic patients, Lipoprotein (a) was found to be an independent risk factor for PAD. The optimal cutoff calculated was 13.3 mg/dl. Patients with Lp (a) above this value were found to have a 2.7-fold higher risk of PAD. Lp (a) also significantly increased from absence of PAD to mild and severe PAD ($P < 0.001$) (84).

A few sporadic cases of Thromboangiitis obliterans have been described in which elevated levels of lipoprotein (a) were reported (35, 85). A 39 year old woman with only involvement of the chest involving both coronary arteries and internal thoracic arteries was reported to have elevated lipoprotein (a) level. In this case the diagnosis was made

by the histological examination of the internal thoracic arteries discarded at surgery which showed thrombotic occlusion and characteristic intimal microabscesses with intact internal elastic lamina and tunica media (35). Biasi et al described a 35 year old male heavy smoker with Buerger's disease who had high level of lipoprotein of 1010mg/L (normal <200) (85). Very high level of Lipoprotein (a) has been reported in a case of Buerger's disease from Italy by Biasi et al almost two decades ago (13).

Kubo et al while investigating Lp (a) levels in CVD patients reported higher levels of Lp(a) in cases of Thromboangiitis obliterans (26.5mg/dl) compared to controls with risk factors (15.4mg/dl) and healthy controls (11.3mg/dl). (86). Takami et al from Japan conducted a study in male subjects to determine whether Lp (a) contributes to the marked increase in cardiovascular diseases without atherosclerotic lesions (10). Serum Lp(a) levels were measured 40-69 years old males with ischemic heart disease (IHD) with normal coronary angiogram (n = 35) and subjects with arteriosclerosis obliterans (n = 123) and IHD with atherosclerotic coronary lesion (n = 203) in addition to patients with Thromboangiitis obliterans (n = 40) and healthy controls (n=156). The levels were significantly higher in all the groups compared to the controls. The Lp (a) level of Thromboangiitis obliterans patients was found to be also much more elevated (21.3 mg/dl) than that of the healthy control group (9.4mg/dl) ($P < 0.05$).

In a recent study on the prevalence of genetic and environmental vascular risk factors in non diabetic patients with premature peripheral arterial disease, either peripheral arterial occlusive disease or Thromboangiitis obliterans, the two main types of peripheral arterial disease, cases of peripheral arterial occlusive disease had much more elevated levels (57.5mg/dl) compared to controls (p value 0.02). But unlike in the previous reports, there

was no significant difference in the Lp (a) values between cases of Premature peripheral arterial disease and controls and also between TAO (32.5 mg/dl) and controls (25.7mg/dl). (23).

Raised levels of Lp (a) has also been seen with increased frequency in cases of Primary Antiphospholipid syndrome (87).

Therapeutic considerations

A few studies have quoted a desirable serum level of Lp (a) of <50mg/dl and others have suggested < 30 mg/dL (75). Niacin has been shown to have an effect in reducing serum Lp (a) levels in coronary artery disease in a Caucasian population. Combination therapy with neomycin (2 g/day) and niacin (3 g/day) in hyperlipoproteinemic subjects caused a 48% decrease in LDL cholesterol levels and a 45% decrease in the concentration of lipoprotein (a) thus altering the progression of cardiovascular disease (14). A meta-analysis of the effect of nicotinic acid revealed a reduction in major coronary events by 27% which could be attributable to decline in plasma LDL cholesterol and Lp(a) concentrations (88). Niacin can reduce lipoprotein (a) concentration in a dose dependent fashion by about 20-30%. In yet another study, it has been reported to decrease lipoprotein (a) concentration by 38% (89). Niacin acts by inhibiting Triglyceride synthesis in the hepatocyte, which causes an accelerated intracellular degradation of hepatic apo B and the reduced secretion of VLDL and LDL particles (90).

A recent meta-analysis has suggested that atorvastatin may also lower Lp (a) levels (91). Similarly other uncommonly used molecules like acetylsalicylic acid and L-carnitine as well as some medications in development including anti-sense oligonucleopeptides (mipomersen), and proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors; Cholesterol-ester-transfer protein (CETP inhibitors) can reduce the elevated lipoprotein (a) concentrations. (92). The effect of estrogen on lipoprotein (a) levels is not well understood. Estrogen replacement therapy in many post-menopausal women suggests an association with lower lipoprotein (a) levels. Till date estrogen has not been indicated for treatment of elevated levels of lipoprotein (a).

Thyromimetics or Thyroid hormone analogs have also been tried to attempt to reduce levels of Lp (a). These thyroid hormones stimulate thyroid hormone receptors (TR) that have usually different tissue distribution and metabolic targets. TRβ is found predominantly in the liver. It has a major role in the metabolism of cholesterol and lipoproteins. TRα has its major role in fat, muscle, and the heart. Thyromimetics have been formulated which activate TRβ and are selectively taken up and/or activated by the liver. These molecules stimulate LDL receptors in the liver. They also induce cholesterol elimination as bile acids and cholesterol, and probably promote reverse cholesterol transport. In animals, they stop or slow down atherosclerotic progression. In humans, eprotirome, a thyromimetic has favorable lipid-modulating effects but lacks thyroid hormone-related side-effects. It also maintains normal hypothalamic-pituitary-thyroid feedback. When used in conjunction with statins, it decreases LDL and non-HDL cholesterol, apolipoprotein B, and triglycerides as well as lipoprotein (a) (93). It is not

clear whether the decrease in lipoprotein (a) reduction also points to reduced cardio vascular morbidity or mortality.

In patients with vascular conditions, the effects of eicosapentaenoic acid (EPA) on serum lipoprotein (a) and other lipid levels were studied. The findings showed that long-term administration of EPA may reduce Lipoprotein (a) and serum lipids, which is of benefit for patients with various arterial occlusive diseases in terms of preventing progression of the disease.(94) Gingko biloba extract may be beneficial in cardiovascular high risk patients, but has not been clinically verified (95).

Lipid apheresis causes excellent short term reduction of lipoprotein molecules and is indicated in cases, such as familial hypercholesterolemia, or treatment resistant hypercholesterolemia. (96). But this is extremely expensive and impractical for most other patients. Niacin being the exception, the currently available drugs have minimal effect on lipoprotein (a) levels.

Currently, the recommended treatment for an elevated lipoprotein (a) in cardiovascular high risk patients is niacin, 1-3 grams daily, generally in an extended release form. Aspirin may be beneficial as well. The goal of treatment is to achieve levels to below 50 mg/d (75). A similar recommendation is not available for management of patients with Thromboangiitis Obliterans.

MATERIALS AND METHODS

The study was conducted in Christian Medical College, Vellore in the department of General Surgery. It was a case control study with cases defined as patients diagnosed to have Buerger's disease according to Shionoya's criteria. The controls were all the patients admitted after the index case and who were under the age of 50 years and were matched for gender. The study period was from 1st August 2011 to 30th September 2013. This study was undertaken after obtaining Institutional Review Board approval.

Once a patient, either a case of Buerger's disease or a control was recruited, informed consent was taken for collection of a fasting blood sample. Every patient was given a patient information sheet which described the study and its purpose and benefits. A detailed history was taken and a thorough physical examination was done. History of smoking and its duration, and any drug intake, and previous operations were also noted down. All the peripheral pulses were documented. Ankle Brachial Pressure Index and Toe Pressures and findings from imaging studies were documented.

A fasting morning (6 AM) blood sample (2ml) was taken for estimation of Lipoprotein (a) levels. The sample was immediately taken to the biochemistry laboratory and processed. The method used for estimation of lipoprotein (a) level was immunoturbidometry. The analyzer used was a Roche p800 Modular. The unit of measurement was mg/dL.

The data thus obtained was statistically analyzed. The cases and controls were compared for demographic data and lipoprotein values. The cases of TAO were categorized into different groups based on Lp (a) levels into those with <30mg/dl, and > 30 mg/dl. The groups were compared for severity of disease with Lp (a) levels. The statistical tests used were Pearson's Chi square, T-test and Kruskal Wallis test. The level of significance was taken as a P value <0.05.

RESULTS AND ANALYSIS

A total of 45 patients each among Thromboangiitis patients (cases) and control groups were enrolled in the study.

Table – 1

AGE DISTRIBUTION AMONG CASES AND CONTROLS

AGE (YEARS)	CASES No.	CASES %	CONTROLS No.	CONTROLS %
<25	3	6.7	10	22.2
25-29	4	8.9	8	17.8
30-34	4	8.9	9	20.0
35-39	9	20.0	5	11.1
40-44	9	20.0	8	17.8
45-49	9	20.0	5	11.1
>50	7	15.6	0	0
TOTAL	45	100	45	100

With Yates correction chi square= 11.179 df =6 p=0.082 Not significant (p>0.05)

Table – 1 (Fig- 1)shows the age distribution among study group and control groups. There were 3 cases (6.7%) of Thromboangiitis obliterans below 25 years of age, while 10 controls (22.2%) were below 25 years. There was no statistically significant difference in the age groups between cases and controls. (p >0.05)

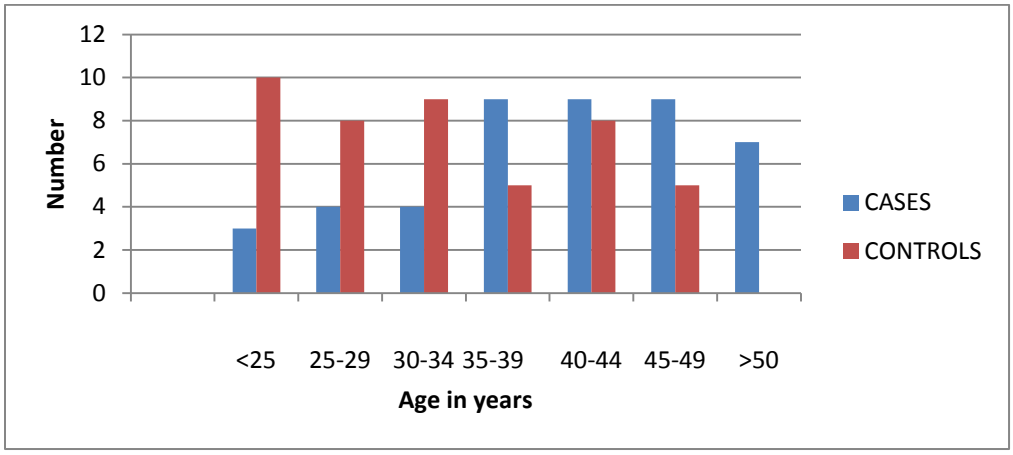


Figure 1

Age Distribution among Cases and Controls

Table – 2

SEX DISTRBUTION AMONG CASES AND CONTROL GROUPS

	Males		Females	
	No.	%	No.	%
Cases (n=45)	45	100	NIL	0
Controls (n=45)	45	100	NIL	0

Table – 2 shows the sex distribution in this study. All the 45 patients (100%) among both cases and control groups were males.

Table – 3

REGIONAL DISTRIBUTION OF CASES AND CONTROLS

Region	Cases No. (%)	Controls No. (%)
South*	17 (37.8%)	27 (60.0%)
West	0	1 (2.2%)
East**	25 (55.6%)	14 (31.1%)
Bangladesh	3 (6.7%)	3 (6.7%)
Total	45 (100.0%)	45 (100.0%)

* p=0.035 ** p=0.0193

Table – 3 (Fig-2, Fig-3) shows the regional distribution among cases and controls. Significantly more number of patients came from the eastern region, (55.6%) compared to the controls (31.1%), (p value 0.0193). Among cases and controls an equal number were from Bangladesh. Among the controls, the majority (60%) was from the south compared to patients with TAO (37.8%), (p value 0.035).

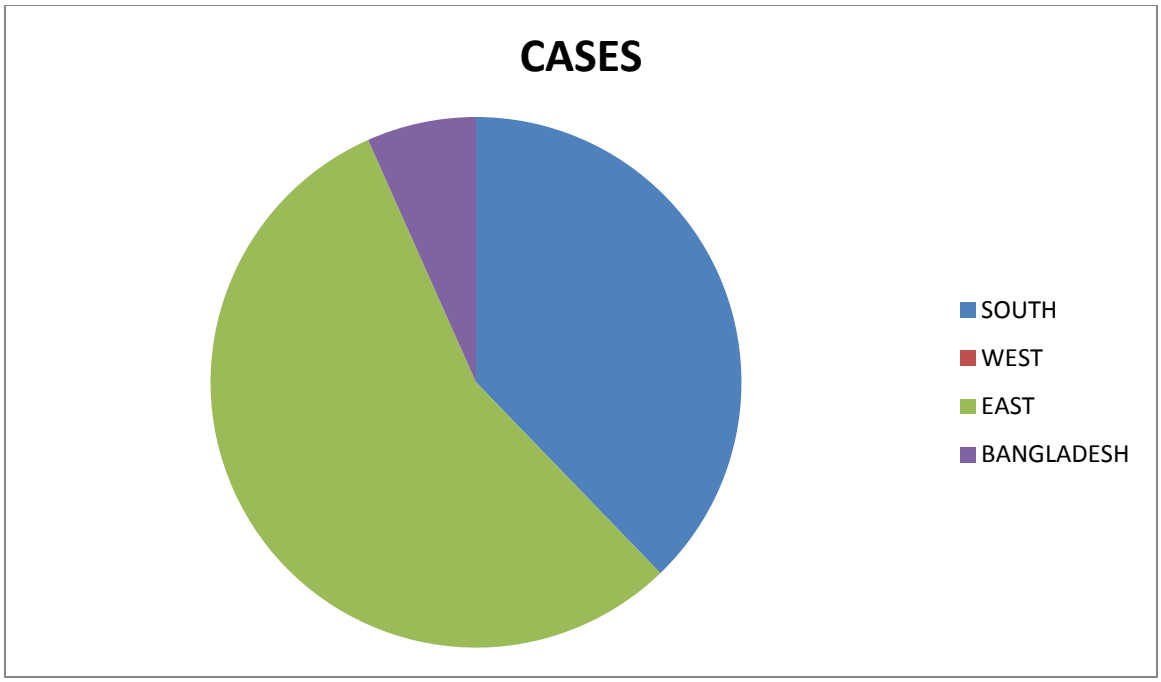


Figure 2 - regional distributions of cases

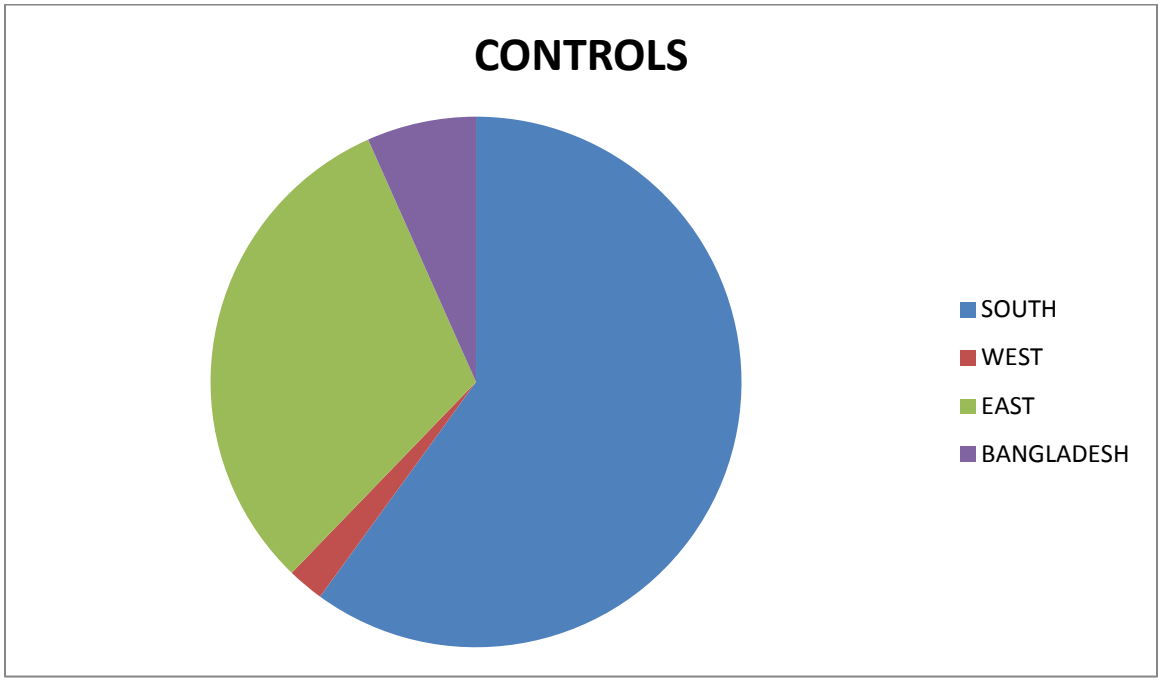


Figure 3 - Regional distribution of controls

Table – 4

NUTRITIONAL STATUS AND CHRONIC DISORDERS

	Cases		Controls		Pearson's Chi sq	P value
	No=45	%	No=45	%		
Under nutrition	7	15.6	3	6.7	1.800	0.180
Diabetes	6	13.3	2	4.4	1.111	0.292
Hypertension	5	11.1	1	2.2	1.394	0.238

Table – 4 shows the prevalence of malnutrition and chronic diseases such as diabetes and hypertension in the 2 groups. There was no statistically significant difference in the prevalence of any of these morbidities between the cases and controls.

Table – 5

ADDICTIONS AMONG CASES & CONTROLS

ADDICTIONS	cases		Controls	
SMOKING*	**No=45**	**%**	**No=45**	**%**
Present	41	91.11%	4	8.89%
Absent	1	2.22%	41	91.11%
not known	3	6.67%	0	0
TOBACCO CHEWING**	**No=45**	**%**	**No=45**	**%**
Present	10	22.22%	3	6.67%
Absent	32	71.11%	42	93.33%
not known	3	6.67%	0	0.00%

*X^2 = 68.495, df = 1, p = 0.000 ** X^2= 5.023, df = 1, p=0.025

Table – 5 shows the prevalence of smoking and tobacco chewing among the study group and control group patients. There was very highly significant increased prevalence of smoking among TAO cases (91.11%) compared to controls (8.9%) (p value < 0.0001). Tobacco chewing was also significantly more common among patients (22.2%) than in controls (6.7%), (p value 0.025).

Table - 6

Duration of smoking among patients with TAO

Duration	No.	Percentage
2-4.9 years	3	7.3%
5-14.9 years	8	19.5%
15-24.9 years	12	29.3%
>25 years	13	31.7%
Not Known	5	12.2%
Total	41	100.0%

Table –6 (Fig- 4) shows the duration of smoking in TAO patients. History of smoking for over 15 years was noted in 61% of the patients. Only a minority of cases (7.3%) had smoking history of less than 5 years.

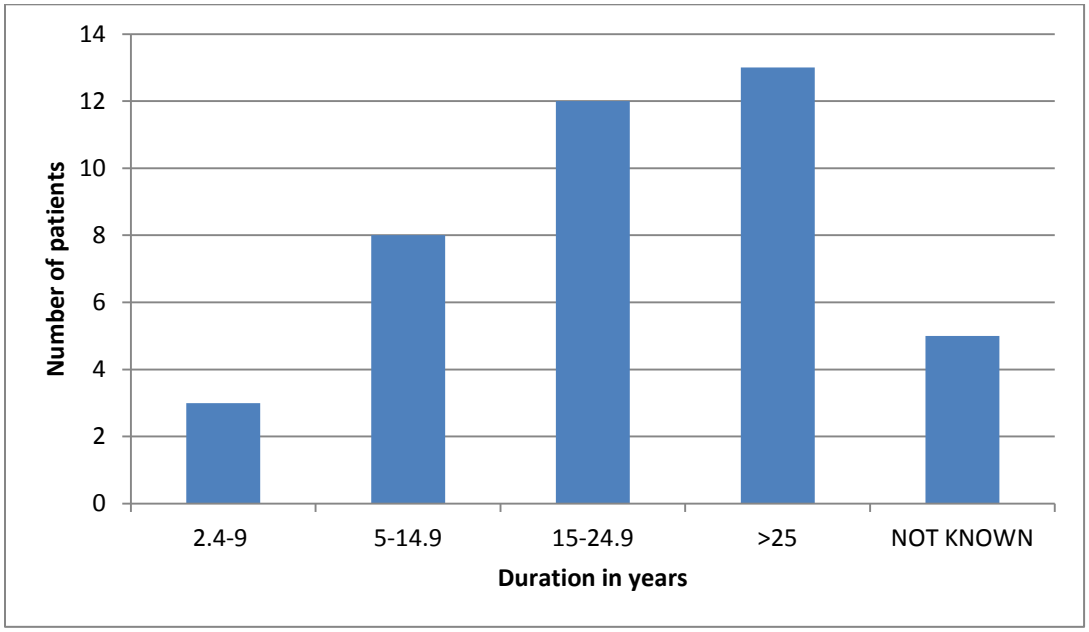


Figure 4 – The duration of smoking among patients of TAO (in years)

Table - 7

PRESENTING SYMPTOMS & THEIR DURATION IN STUDY GROUP

Symptom	No. = 45	Percentage	Mean duration
Claudication	38	84.4%	35.9 months
Rest pain	27	60.0%	2.7 months
Gangrene	36	80.0%	8.7 months
Ulcer	20	44.4%	3.3 months

Table – 7 shows the prevalence and mean duration of symptoms in patients with TAO. Claudication of limbs was present in the majority (84.4%) of patients. Rest pain was observed in 60% of the patients and gangrene in 80%. Claudication had the longest duration, mean value being 35.9 months. The symptom with the shortest duration was rest pain (2.7 months)

Table - 8

PATTERN OF ARTERIAL INVOLVEMENT IN PATIENTS WITH TAO

Arterial involvement	No (45)	Percentage
Infrapopliteal	14	31.1%
Femoropopliteal	19	42.2%
Suprainguinal	12	26.7%
Upper limb	8	17.8%

The pattern of highest level of arterial occlusion is shown in Table 8 (Fig-5) . Infrapopliteal involvement was observed in 31.1% of patients. But when all cases (not only highest levels) are included this increased to 97.8% of cases. Upper limb vessels were involved in 8 (17.8%) of patients.

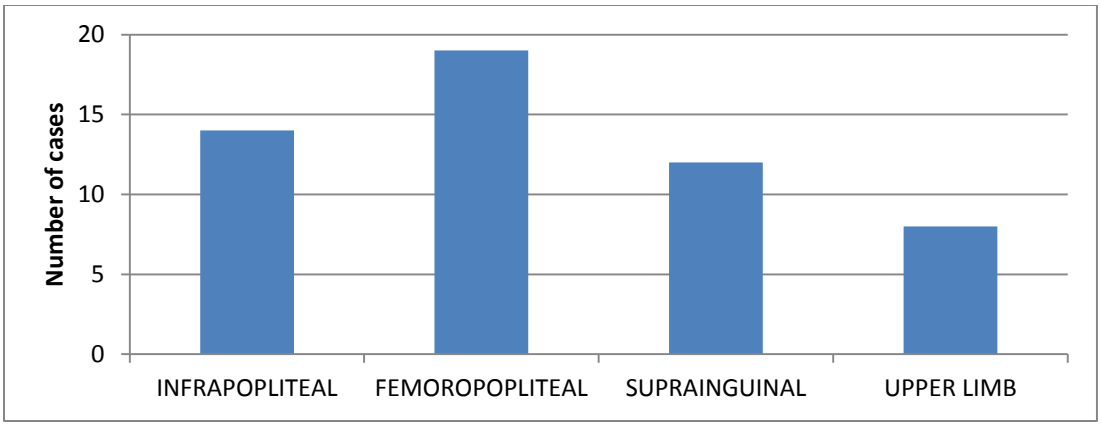


Figure 5

Pattern of vessel involvement in patients of TAO

Table – 9

LIPID PROFILE AMONG CASES

LIPID	mg/dl	No=40	Percentage
Total cholesterol	>160	11	27.5
Triglycerides	>150	5	12.5
HDL cholesterol	<40	29	72.5
LDL cholesterol	>100	12	30.0

Table -9 shows the prevalence of abnormal lipid profile in cases with TAO. Almost 3/4th (72.5%) of patients had low HDL cholesterol, while 27.5% had elevated total cholesterol. The mean Lp (a) for those with total cholesterol >160 mg/dl and <160 mg/dl was 64.4 mg/dl and 61.7 mg/dl respectively and this difference was not statistically significant.

Table -10

ANKLE BRACHIAL PRESSURE INDEX & TOE PRESSURE AMONG CASES

Measurements	No.	%
ABPI		
<0.40	10	22.2
0.41-0.90	24	53.3
>0.9	11	24.4
Toe pressure*		
<40 mmHg	40	88.8
>40 mmHg	4	8.9
Total	45	100.0

*not done in 1 case

The ankle brachial pressure index and Toe pressure in TAO patients is shown in Table – 10. The index was less than 0.40 in 22.2% of the patients and between 0.4 and 0.9 in 24 (53.35%) (Fig – 6). Toe pressure of <40mmHg was seen in 88.8% of cases (Fig – 7).

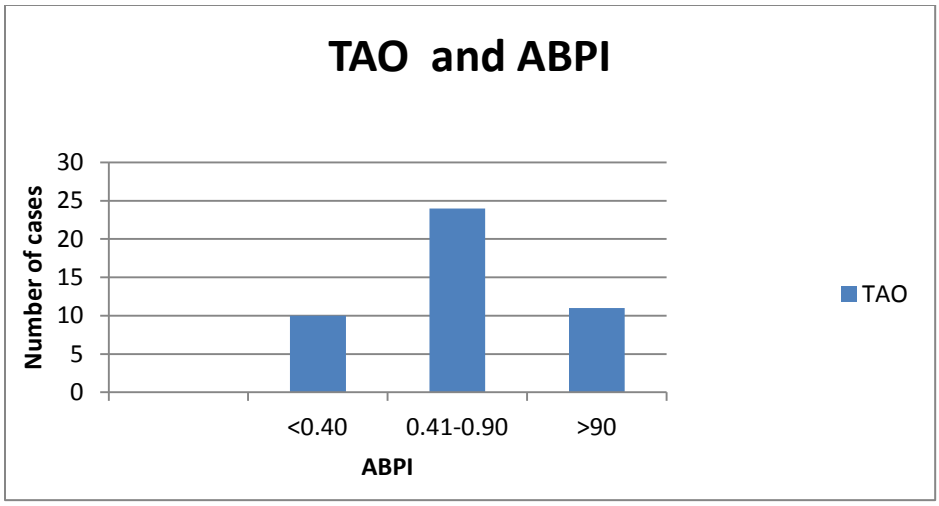


Figure 6 - ABPI among cases

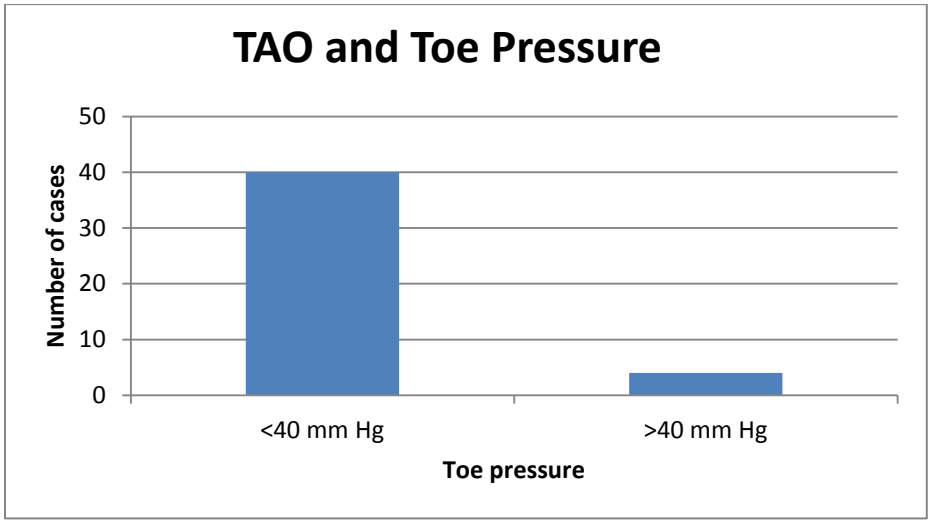


Figure 7 - Toe pressure among cases

Table – 11

Frequency of normal & elevated Lp (a) values among cases and controls

Groups	<30mg/dl	>30mg/dl	Total
Cases count	12	33	45
% within group	26.7%	73.3%	100.0%
% within Lp(a)	46.2%	51.6%	50.0%
Controls count	14	31	45
% within group	31.1%	68.9%	100.0%
% within Lp(a)	53.8%	48.4%	50.0%

Chi square = 0.216 p value = 0.642

Table – 11 (Fig – 8) shows the number of patients with normal (<30) and elevated Lp (a) (>30) values among the 2 groups of cases and controls. There was no significant difference between the 2 groups of cases and controls.

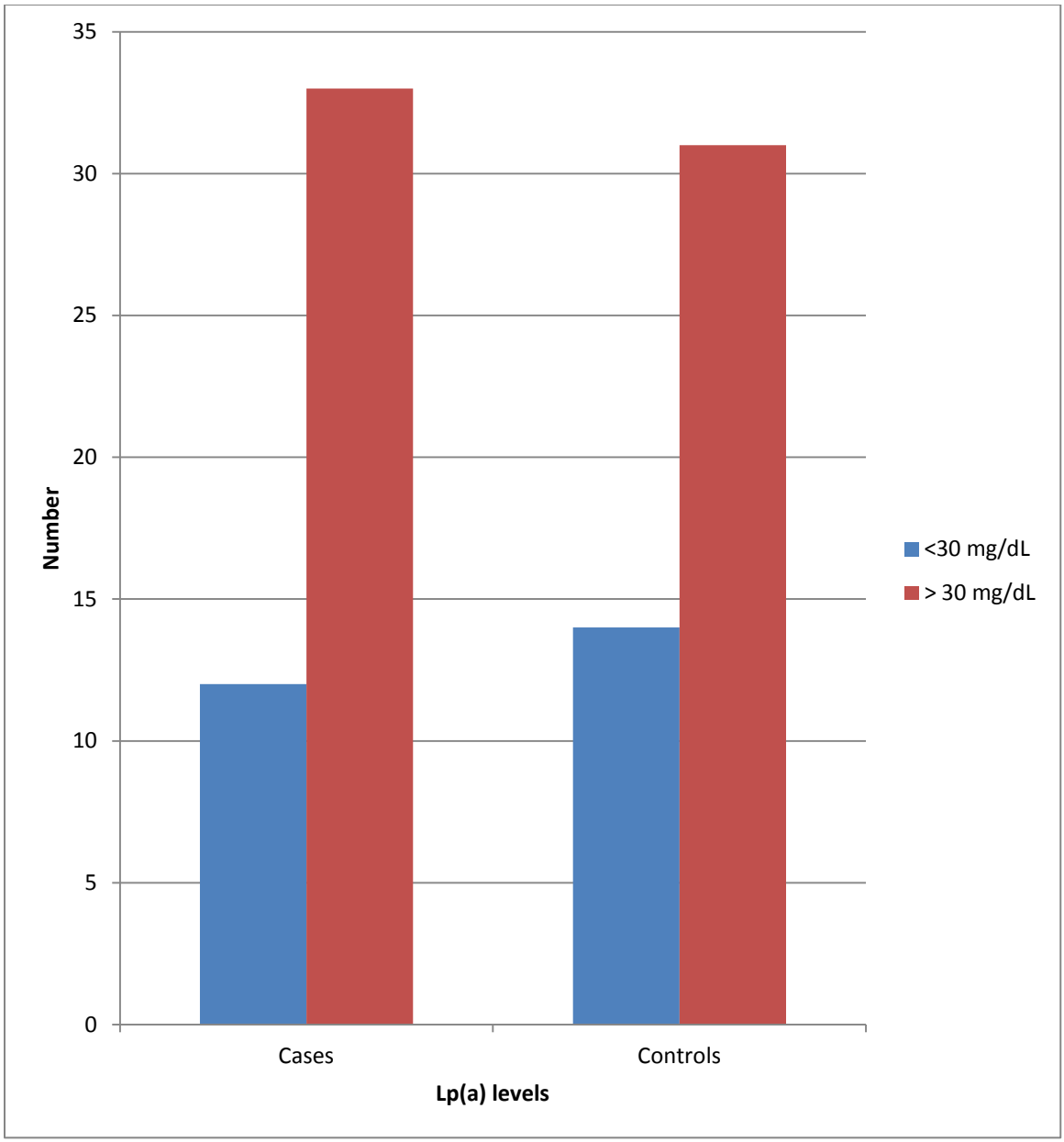


Figure 8

Normal and elevated Lp(a) values among cases and controls

Table-12

Lipoprotein (a) value categories in the cases and control groups

			lpar			
			<30	30-100	>100	Total
group	cases	Count	12	23	10	45
		% within group	26.7%	51.1%	22.2%	100.0%
		% within lpar	46.2%	42.6%	100.0%	50.0%
	controls	Count	14	31	0	45
		% within group	31.1%	68.9%	0.0%	100.0%
		% within lpar	53.8%	57.4%	0.0%	50.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	11.339[a]	2	.003
Likelihood Ratio	15.207	2	.000
Linear-by-Linear Association	4.295	1	.038
N of Valid Cases	90		

Comparisons between

Lp (a) <30 and 30-100 – chi square=0.09, p value = 0.764

Lp (a) <30 and >100 - chi square =6.691 p value=0.0097

Lp (a) 30-100 and >100 chi square = 8.954 p value = 0.0028

Table – 12 (Fig – 9) shows the frequency distribution of various categories of lipoprotein (a) levels among cases and controls. Values less than 30mg/dl were observed in 26.7% of study patients and 31.1% of the controls. **Very high values of Lp (a) were found only in TAO as compared to controls which was statistically highly significant (p=0.003). Very high values above 100mg/dl was seen in none of the controls, while it was observed in 10 patients with TAO (22.2%)**.

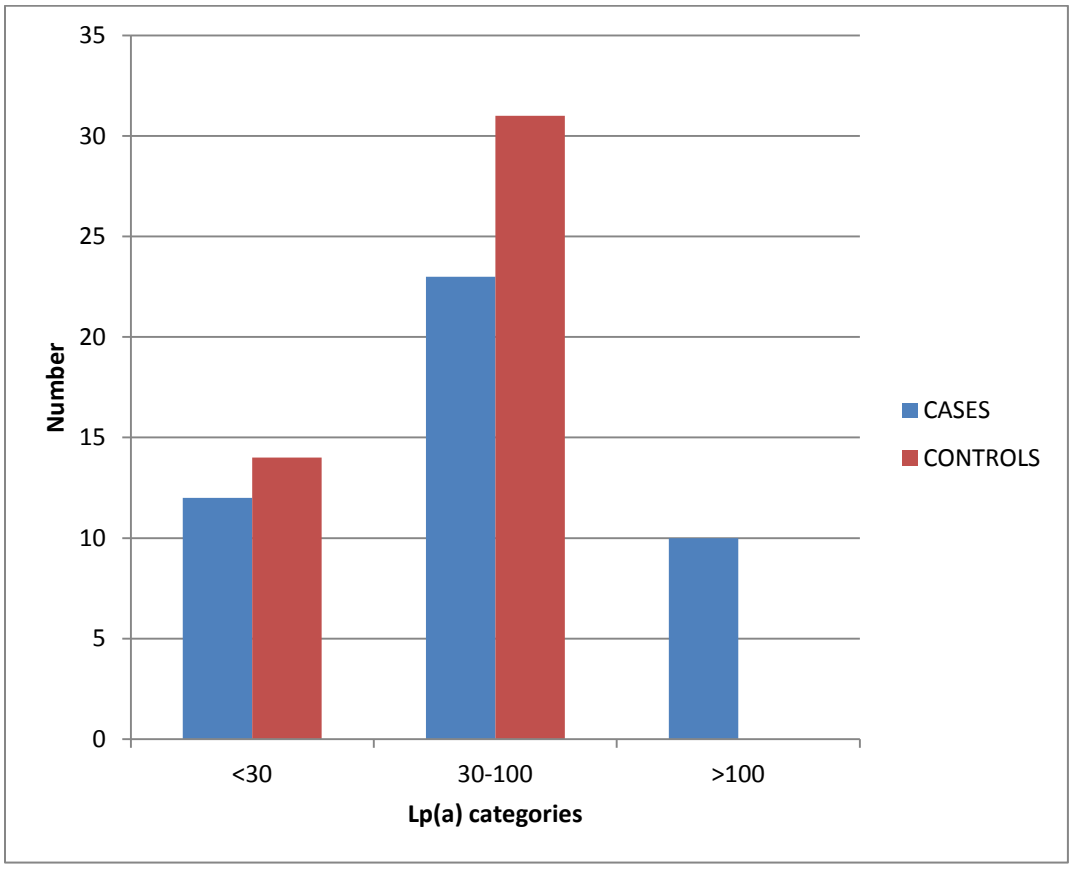


Figure 9 - Lp(a) categories among cases and controls

Table - 13

Mean Lipoprotein values among the 2 groups of cases and controls

Lp (a)	Cases (mg/dl)	Controls (mg/dl)
Mean value	70.194	40.857
Standard deviation	69.425	23.218
Minimum value	<3	<3
Maximum value	354	83.14

t value -2.688 p = 0.0086

Table – 13 shows the mean lipoprotein (a) values among cases of TAO and the controls. The mean value of Lp (a) was significantly higher in cases of TAO (70.19) than in controls (40.86), (p value 0.0086). The maximum level noted among the cases and controls were 354 mg/dl and 83.14 mg/dl respectively. The lowest value was <3mg/dl in both the groups.

Table -14

Association of Lp (a) categories and presence of symptoms

Lp(a)	Claudication No (%)	Rest pain No (%)	Gangrene No (%)	Ulcer No (%)
<30	10 (26.3%)	6 (22.2%)	9 (25%)	6 (30%)
% within Lp(a) N=12	83.3%	50%	78%	50%
30-100	20 (52.6%)	14 (51.9%)	18 (50%)	9 (45%)
% within Lp(a) N=23	87%	60.9%	78.3%	39.1%
>100	8 (21.1%)	7 (25.9%)	9 (25%)	5 (25%)
% within Lp(a) N=10	80%	70%	90%	50%
Total	**38 (100%)**	**27 (100%)**	**36 (100%)**	**20 (100%)**
% within Lp(a) N=45	**84.4%**	**60%**	**80%**	**44.4%**
Chi Square	0.272	0.924	0.856	0.538
P value	0.873	0.630	0.652	0.764

Table – 14 shows the frequency distribution of Lp (a) categories and the presenting symptoms. There was no significant difference in the number of patients with any symptom across various categories of Lp (a) (p=>0.05).

Table -15

Relationship between Mean duration of symptoms, Claudication distance and L p (a) values

Lp(a) Values (mg/dl)	Claudication duration (months)	Claudication distance (meters)	Rest pain duration (months)	Gangrene duration (months)	Ulcer duration (months)
<30	45.8	136	3.9	12.4	2.3
30-99	42.0	358	2.75	3.97	4.08
>100	6.7	129	1.7	14.1	2.7
Total cases	35.9	253	2.7	8.7	3.3
Kruskal-Wallis test Significance (<0.05)	0.201	0.069	0.242	0.588	0.392

Table – 15 shows the mean duration of symptoms and claudication distance in various categories of lipoprotein values. Kruskal-Wallis test for independent samples did not show any significant differences in the duration of symptoms or claudication distance across the various categories of Lp (a) ($p>0.05$).

Table-16

Association between ABPI and Lipoprotein values

ABPI	Lipoprotein values (mg %)		
	<30	30-100	>100
<0.40	1 (8.3)	6 (26.1)	3 (30.0)
0.40-0.90	8 (66.7)	13 (56.5)	3 (30.0)
>0.90	3 (25.0)	4 (17.4)	4 (40.0)

Chi square = 4.393 p value = 0.355

Table – 16 (Fig – 10) shows the association between ABPI and lipoprotein (a) values. There was no significant difference between rising ABPI values and the various categories of Lp (a) (p value = 0.355).

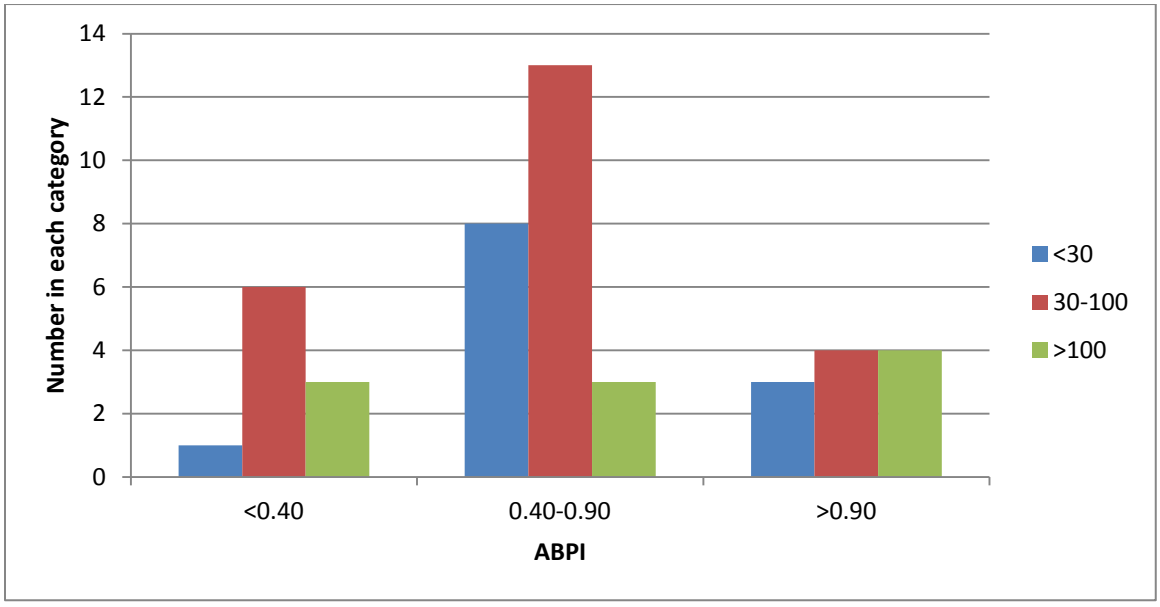


Figure 10

Ankle Brachial Pressure Index & Lp(a) categories among cases

Table -17

Toe Pressure & Lp (a) levels among Cases*

Toe pressure mmHg	Lp(a) <30 mg/dl	Lp(a) 30-100 mg/dl	Lp(a) >100 mg/dl
<40	12 (100%)	21 (91.3%)	7 (77.8%)
>40	0 (0%)	2 (8.7%)	2 (22.2%)

*Not done in one case

Yates correction, Chi square=1.065 p value=0.587

Table – 17 (Fig -11) shows the association of toe pressure with Lp (a) levels. There was no significant difference in the toe pressure in the 2 groups with increasing levels of Lp(a).

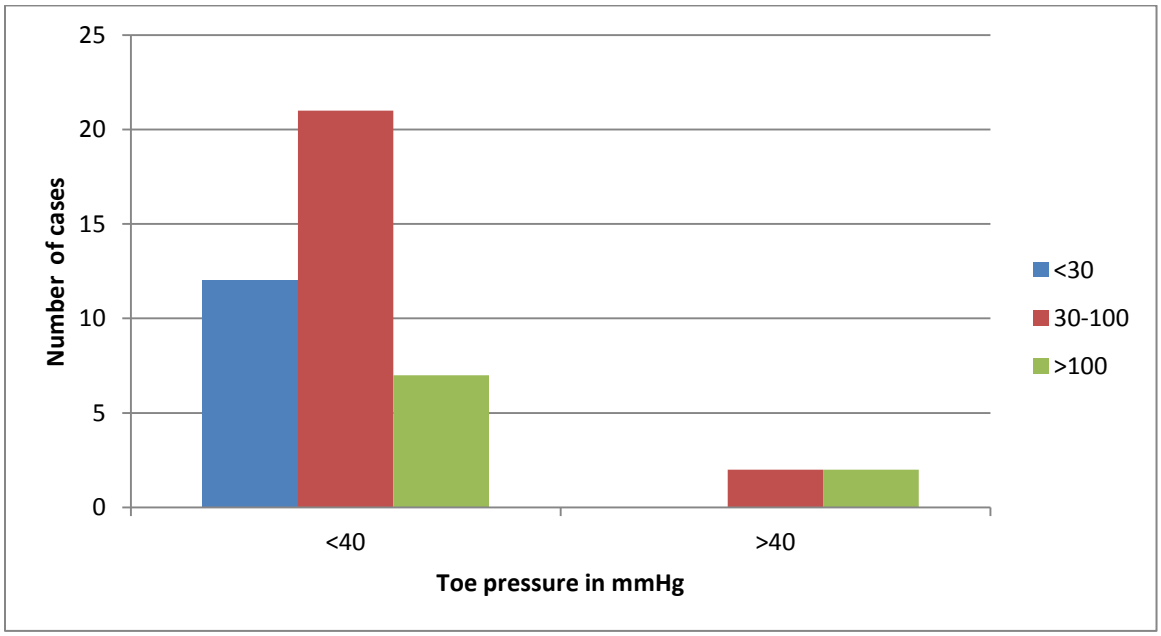


Fig 11

Toe pressure & Lp(a) values

Table 18

Pattern of vessel involvement and Lp (a) values

Vascular involvement	<30	>30	Total		X^2	P value
Infrapopliteal (IP) % of vascular % of Lp(a)	3 (21.4%) (25%)	11 (78.6%) (33.3%)	14 (100%) (31.1%)	IP v/s FP	0.416	0.680
Femoropopliteal(FP) % of vascular % of Lp(a)	6 (31.6%) (50%)	13 (68.4%) (39.4%)	19 (100%) (42.2%)	IP v/s SI	0.132	0.896
Suprainguinal (SI) % of vascular % of Lp(a)	3 (25%) (25%)	9 (75%) (27.3%)	12 (100%) (26.7%)	IP v/s UL	1.127	0.273
Upper limb (UL)* % of vascular % of Lp(a)	2* (25%) (16.7%)	6* (75%) (18.2%)	8* (100%) (17.8%)	FP v/s SI	0.278	0.783
Total % of vascular % of Lp(a)	12 (26.7%) (100%)	33 (73.3%) (100%)	45 (100%) (100%)	FP v/s UL	0.654	0.519
				SI v/s UL	0.99	0.333

*Cases with UL involvement had in addition lower limb involvement

Table – 18 (Fig – 12) shows the pattern of vessel involvement in various categories of lipoprotein values. There was no significant difference between any of the groups with regard to the level of vascular involvement and Lp (a) values (p=>0.05)

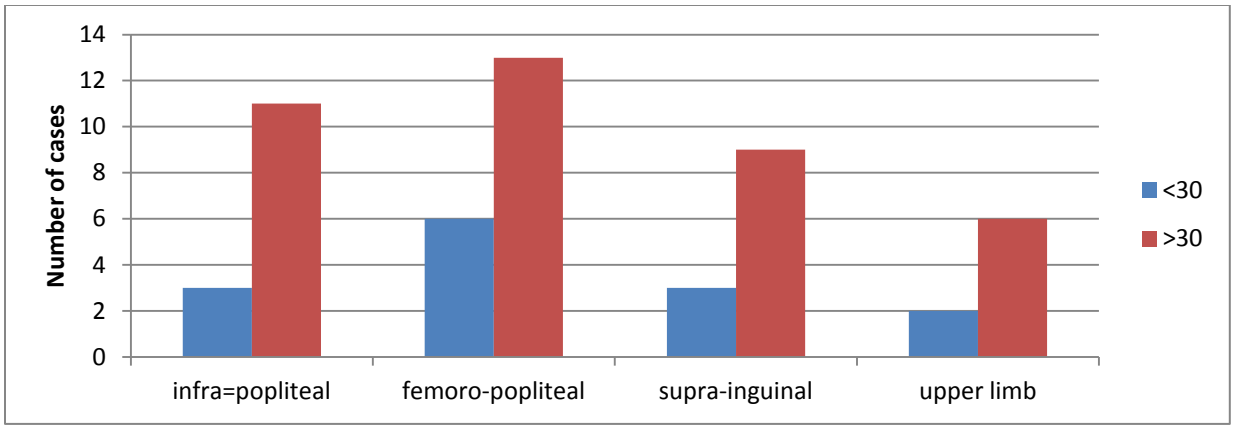


Figure 12

Pattern of vascular involvement and Lp(a) levels

Table - 19

TREATMENT MODALITIES AMONG CASES

TREATMENT		n=45	Percentage	Mean Lp(a)	P value
Conservative		12	26.67	66.34	0.78
Single procedure		22	48.89	50.5	0.054*
Multiple procedures		11	24.44	113.7	
Lumbar sympathectomy		12	26.67	90.55	0.245
Angioplasty & Stenting		5	11.11	33.72	0.0092
Surgical	Amputation	13	28.89	120.81	0.0148
	Bypass	11	24.44	55.12	0.303
	Miscellaneous	6	13.33	93.71	0.333

*comparison between single and multiple procedures.

Table -19 shows the various modalities of treatment offered to the patients in the study group. Conservative therapy was carried out in 12 (26.7%) patients. Eleven patients (24.4%) had multiple surgical procedures. Amputation was performed in 13 (28.89%) and bypass surgery in 11 (24.44%) patients. Patients who underwent amputation had significantly higher level of Lp (a), p=0.0148. Patients who had single procedure had

lower mean level of Lp (a) compared to those who had multiple procedures (50.5mg/dl versus 113.7mg/dl), though statistically the difference was not significant (p=0.054).

Table -20

Risk of amputation among Lp (a) level categories

Lp(a) values (mg/dl)	Amputations done		Amputations not done		Total
	No	%	No	%	
<30	1	8.3%	11	33.3%	12 (26.7%)
>30	12	91.7%	21	66.7%	33 (73.3%)

Chi square = 2.139 p= 0.144

Table -20 (Fig - 13) shows the risk of amputation among those with normal levels compared to those with abnormal levels of Lp (a). There was no significant difference between the 2 groups.

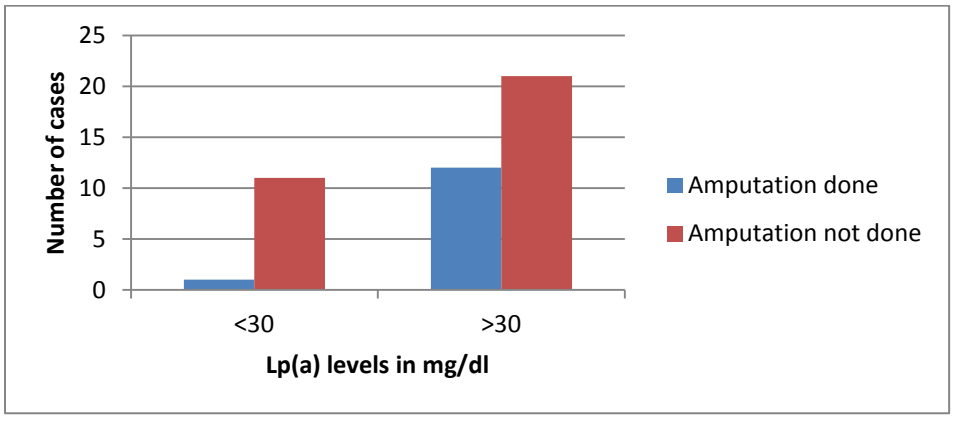


Figure 13 - Amputation and Lp(a) levels

Table-21

RISK OF AMPUTATION AMONG CATEGORIES OF LP (a) VALUES

Lp(a) values (mg/dl)	Amputations	
	No	%
<30 (n=12)*	1	8.3%
30-100 (n=23)**	5	21.7%
>100 (n=10)***	7	70.0%

Pearson's Chi square =11.268 p value = 0.004

Comparison between * & ** chi square=0.277, p = 0.599

Comparison between * & * chi square=6.497, p=0.011**

Comparison between ** & * chi square=5.085, p=0.024**

Table – 21 (Fig -14) shows the risk of amputation in relation to various categories of Lp (a) values. It was 70% in those with Lp (a) levels above 100mg/dl, significantly more

than in those with lesser values (p=0.004).

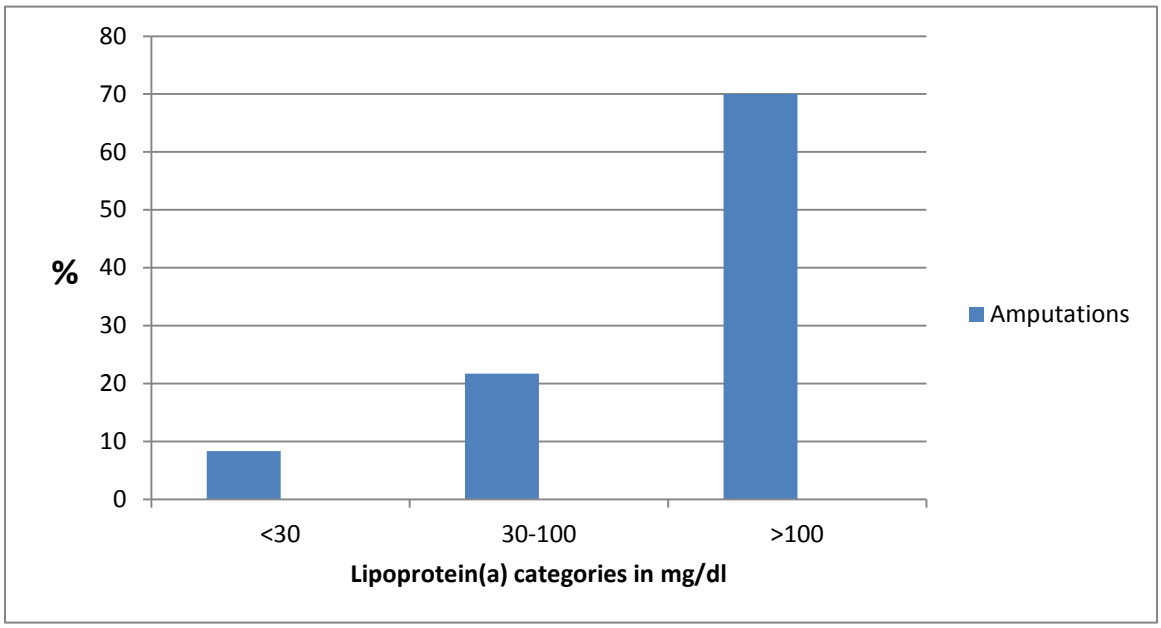


Fig 14 - Risk of amputation and Lp(a) categories

Table - 22

Mean Lp (a) values among amputees and non-amputees

	Mean value of Lp(a)	Std deviation	Significance value
Amputation done	120.82	49.63	T value = 2.75 P = 0.0148
Amputation not done	49.63	48.28	

Table – 22 shows that the mean Lp (a) value was significantly higher in the amputees compared to the non-amputees (p=0.0148).

Summary of Results

A total of forty five cases and forty five controls were recruited for the study and their serum lipoprotein (a) levels were measured.

30 mg/dL was taken as the normal cutoff.

The levels of Lp (a) were not found to be significantly higher in the cases as compared to controls (p value = 0.642) .

When Lp(a) levels were categorized into 3 groups <30mg/dl, 30-100mg/dl and >100mg/dl, there was significantly more cases with higher values compared to controls. This can be attributed to the very high values (>100mg/dl) found only in the patients with TAO and not amongst controls.

Importantly, the mean value in the cases was significantly higher (70.19mg/dl) than in the controls (40.86mg/dl) (p value 0.0086).

There was no association between duration of symptoms like claudication, rest pain, gangrene and ulcer and Lp(a) levels. (p 0.201, 0.242, 0.588 and 0.392)

There was also no association found between ABPI and Toe Pressures and levels of Lp(a) p value = 0.642) and between pattern of vascular involvement Lp(a) levels.

Another point of interest was that patients who had very high values of lipoprotein (a) (>100mg/dl) had a significantly higher risk of amputation (p=0.011).

DISCUSSION

Thromboangiitis obliterans (TAO) is a segmental, recurrent, inflammatory, obliterative vascular disease involving medium-sized arteries and veins of the limbs characterised by thrombosis and recanalisation of the involved vessels.

The majority of the patients (64.4%) were under 45 years of age (Table – 1). There was no significant difference in the frequency distribution of various age groups among cases and controls ($p > 0.05$). The mean age in our study was 41 ± 10 years, very similar to that by Olin et al in which the mean age was 42 ± 11 years.(5) Our findings are comparable to the diagnostic criteria of Olin (2) where the age is predominantly under 45 years and Shionoya (22) in which the age is under 50 years. But in the report by Matsushita et al the mean age was slightly lower (36 ± 8 years) (16) and in the study by Cooper et al it was even lower (33 years $\pm$ 8) (39).

All the patients were males in our study (Table – 2) which is similar to literature reports in which males represent over 90% of affected cases (4) and in a report from Japan 96% of cases were found to be males (16). A rising trend in women has been reported which is attributed to the increased prevalence of smoking in women (15).

Table – 3 shows the regional, distribution of cases. Majority of our patients were from the east, 55.6% from eastern region of India and 6.7% from an eastern country, Bangladesh. This is again similar to what has been described previously, where the highest incidence is seen in the Far East (3). Another reason could be that our institution

is a preferred centre for tertiary care by the patients from eastern India especially West Bengal.

The prevalence of under nutrition and chronic diseases like diabetes and hypertension were similar in the cases and control groups (Table-4-). Hypertension was observed in 5 (11.1%) of patients with TAO. Cooper et al reported 8.1% of patients with hypertension (39). There was very highly significant increased prevalence of addictions among the cases compared to the controls (Table – 5). Smoking was observed in 91.1% and 8.9% among cases and controls (p value 0.0000). Similarly tobacco chewing was also significantly more among cases, (p vale 0.025). This is in accordance with the known fact of a strong link between tobacco consumption and disease (22), and the typical patient being a heavy smoker and tobacco consumption being central to the initiation and progression of the disease (3). Even without smoking, tobacco chewing itself is a risk factor for the development of Thromboangiitis obliterans (36).

Table – 6 shows the duration of smoking among the cases, majority were chronic smokers, 61% having smoked for over 15 years. Our study is consistent with the extremely strong association between heavy use of tobacco and TAO (2).

In the current study (Table – 7), the commonest symptom was claudication observed in 84.4% of patients, higher than that reported by Szuba et al, varying from 18% to 63% (4). In the study by Malecki et al, claudication was observed in 44% of patients. Gangrene and ulcer were noted in 80%, and 44.4% respectively. This is much higher than that reported by Malecki et al from Poland (7%) (38) but this is comparable to 50-81% reported by Szuba et al (4). Rest pain was observed in 60% of our cases compared to the study by Olin et al where it was 76% (5). But Malecki et al reported a much lower incidence of 9% rest pain in cases of TAO (38). At presentation the longest duration was for claudication (mean 35.9 months) and the shortest for rest pain (2.7 months) and non healing ulcer (3.3 months). This is because pain even at rest which is indicative of critical limb ischemia motivates a patient to seek treatment from a tertiary care centre.

The pattern of arterial involvement at the highest level is shown in Table -8. Infrapopliteal involvement was seen in 31.1%, and upper limb involvement in 17.8% cases in our study. This is lower than other reports where lower extremity involvement was reported in 46% by Olin et al (5). Malecki et al have reported 100% affection of lower limbs irrespective of involvement at a higher level. (38). This is similar to our findings of 97.8% involvement when all levels are considered. Upper limbs were involved in 17.8% of our patients which is lower than 44% reported by Malecki et al (38).

Infra popliteal involvement has been reported in 90 -100% of patients in literature (4). Upper limb involvement has been higher 38% as reported by Mills et al (97) and 50% among affected women in the study by Lie (15). Malecki et al has reported 100% of lower limb involvement and 44% of upper limb involvement (38).

An Ankle Brachial Pressure Index of 0.40 or less, which is considered as a marker of critical limb ischemia by the American Diabetes Association was observed in 10 (22.2%) of cases (Table – 10) (98).

Table – 11 which shows the frequency distribution of normal and elevated levels of Lp (a) showed no significant differences between cases and controls. But as shown in Table – 12 when those with Lp(a) levels above 30mg/dl were classified further into those above 100mg/dl and those between 30 to 100mg/dl, there was a significantly more number of cases with elevated levels than controls. (p= 0.003). This implies that patients with markedly elevated serum lipoprotein (a) levels are more likely to be at risk of developing TAO. The frequency of markedly elevated lipoprotein (a) level is 22.2% in this study. This can be compared to the study by Murase et al where markedly elevated Lp(a) levels had an impact on the risk of CAD and the frequency was 6.4% in cases of familial hypercholesterolemia and 0.9% in diabetes (99).

The mean lipoprotein(a) value of the cases (70.19) was significantly higher than that of the controls (40.86), p value 0.0086 as shown in Table – 13, which is similar to earlier reports (17, 86). According to Takami et al, the level observed was 23.1mg/dl in their patients with TAO, but this is much higher in our study (17). In the report by Kubo et al the Lp (a) levels in TAO patients was 26.5 mg/dl as against 15.4 mg/dl in controls. This again is much lower than what has been observed in this study. The highest level noted in our study was 354mg/dl which is three times higher than the level of 1010mg/L (101mg/dl) which has been reported in a case of Buerger's disease from Italy (85). According to Nordestguard et al, lipoprotein (a) level may vary up to a 1000 fold even in normal individuals (100).

A high level of total cholesterol >160mg/dl and LDL-cholesterol >100mg/dl was observed in 27.5% and 30% of patients respectively (Table -9). But Cooper et al observed hyperlipidemia in a greater proportion (46.5%) of cases with TAO (39). There was no significant difference in the mean Lp (a) levels of patients with high and normal total cholesterol levels in the current study. But in a study from Taiwan there was a significant association of total cholesterol and LDL cholesterol with serum Lp (a) levels (101).

The prevalence and duration of symptoms of claudication, rest pain, gangrene and ulcer, had no significant association with the Lp (a) values. (Table-14 & 15). ABPI and Toe pressure measurements also did not have any association with serum Lp (a) values (Table – 16, 17). Both ABPI and Toe pressure which are measures of severity of arterial occlusion showed no association with Lp (a) levels. These probably indicate that that there is no association between severity of disease as measured by ABPI and Toe pressures, and serum Lp (a) levels. The pattern of vessel involvement did not reveal any relationship with Lp (a) levels (Table – 18).

Conservative management and lumbar sympathectomy were done in 12 patients each (26.7%). Bypass was performed in 11 (24.4%) and amputation in 13 (28.9%). Mills et al reported an incidence of 31% for amputations (97). In the study by Cooper et al, the risk of any extremity amputation was 25% at 5 years (39). Major amputation defined as above-the-knee, below-the-knee or hand amputation was performed in 4 patients (8.89%) in our series. The rate of major amputation was 3.9% in the study by Ohta et al (102).

According to the report by Cooper et al, the risk of major amputation at follow-up at 5 years, 10 years and 20 years was 11%, 21% and 23% respectively among TAO patients who continued smoking (39). After smoking cessation only 2 out of 89 (2.2)

underwent amputation according to the study by Olin et al (5). The mean Lp (a) value was significantly higher in those undergoing amputation, 120.81 mg/dl versus 49.63 mg/dl (p value 0.0148). With rising Lp (a) levels there was increasing risk of amputations (table – 20) (p value 0.00275). This is suggestive of an association between severity of disease and the Lp (a) levels.

LIMITATIONS OF THE STUDY

The exact role of lipoprotein in thrombogenesis is not well understood. It may well be an inflammatory marker in chronic diseases.

The population studied may not be representative of the country. Most of the cases were from the eastern region.

The role of smoking on lipoprotein cannot be commented upon as smoking was not taken into consideration for choosing controls.

The sample size calculated is very small.

The acceptable level of lipoprotein (a) has been debated and there is no agreed upon "normal value". In our study it has been taken as < 30 mg/dL. Other studies say a value of less than 50 mg/dL is the target.

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